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OSE Integrated Review

Date:	July 5, 2018
Reviewer(s):	Sarah Kang, PharmD, Safety Evaluator Ofir Noah Nevo, PharmD, Safety Evaluator Robert Levin, M.D., Lead Medical Officer for Pharmacovigilance Strategy *Division of Pharmacovigilance I* Daniel Bak, PharmD, Drug Utilization Analyst *Division of Epidemiology II* Andrew Mosholder, M.D., Medical Officer *Division of Epidemiology I*
Team Leader(s):	Vicky Chan, Pharm.D, BCPS, Safety Evaluator Team Leader *Division of Pharmacovigilance I* Travis Ready, PharmD, Drug Utilization Analyst Team Leader *Division of Epidemiology II* Kira Leishear, PhD, MS, Lead Epidemiologist *Division of Epidemiology I*
(Deputy) Division Director(s):	Cindy Kortepeter, PharmD, Director *Division of Pharmacovigilance I* Grace Chai, PharmD, Deputy Director for Drug Utilization *Division of Epidemiology II* Sukhminder Sandhu, PhD, MPH, MS, Deputy Director *Division of Epidemiology I*
Product Name:	Nuplazid (pimavanserin)
Subject:	Death and Other Adverse Events of Interest

Application Type/Number:	NDA 207318
Applicant/Sponsor:	Acadia
OSE RCM #:	2018-607
TSI #:	1890

**** This document contains drug utilization data provided by the Sponsor that are confidential and for internal FDA purposes only; this information cannot be released or discussed publicly without the Sponsor's approval.****

Special thanks to Dr. Daniel Woronow for his assistance with this review.

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EXECUTIVE SUMMARY

The Division of Psychiatry Products (DPP) consulted the Division of Pharmacovigilance (DPV) to evaluate the FDA Adverse Event Reporting System (FAERS) reports of pimavanserin since approval due to the large number of death reports in Acadia's (the Sponsor) periodic adverse event report, and also highlighted in the Institute for Safe Medication Practices QuarterWatch Report. Additionally, a FAERS data mining analysis by the Division of Applied Regulatory Science suggested risks of autonomic dysfunction, falls and insomnia with pimavanserin. DPP opened a Tracked Safety Issue to address these concerns. This review evaluates the safety profile of pimavanserin using a surveillance summary approach.

Our review did not identify any new safety findings with pimavanserin, compared to the premarketing safety profile. A large proportion (85%) of reports of fatalities and serious adverse events (SAEs) were collected through solicited reporting via a patient support program and specialty pharmacy network, in which the company actively contacts patients and families and inquires about adverse events. Most solicited cases provided insufficient information to assess drug-event causality. Because of limited clinical details and the presence of several underlying patient risk factors, these postmarketing AE reports are challenging to interpret. The controlled trials in Parkinson's disease psychosis (PDP) demonstrated increased rates of all-cause mortality and all-cause SAEs in the pimavanserin group compared to the placebo group. However, there were no unifying adverse events or mechanisms to explain these findings. Several factors contribute to the number and types of postmarketing reports of fatalities and other SAEs with pimavanserin. PD patients in general have a high mortality rate, and PDP is considered an end-stage condition, particularly when associated with dementia and long-term care settings.

In addition, many PDP patients in postmarketing reports were treated concomitantly with other antipsychotics, which further increases the risk of all-cause mortality in PD patients and elderly patients with dementia-related psychosis. Many antipsychotics including pimavanserin can also prolong the QT interval. It is possible that pimavanserin contributed to some of the postmarketing fatal and other SAEs, possibly through QT prolongation or other currently unidentified mechanisms.

Pimavanserin is almost exclusively distributed by specialty pharmacies and specialty distributors. Frequent contact with consumers via reimbursement hubs, patient assistance programs, or specialty pharmacies can explain the high number of postmarketing AE reports for pimavanserin. Drug utilization data and FAERS data showed patients aged 70 years or older accounted for the highest proportion of pimavanserin use.

We recommend revising the Warnings and Precautions and Drug Interactions sections of labeling to emphasize the risks of QT prolongation and serious cardiovascular events, particularly during concomitant use of pimavanserin and other drugs known to cause QT prolongation. We recommend listing specific antipsychotics and antidepressants known to cause QT interval prolongation, which are used commonly in PDP patients. We recommend considering issuing a Drug Safety Communication regarding these risks.

1. INTRODUCTION

The Division of Psychiatry Products (DPP) consulted the Division of Pharmacovigilance (DPV) to evaluate the FDA Adverse Event Reporting System (FAERS) reports of pimavanserin since approval due to the large number of death reports in Acadia's (the Sponsor) periodic adverse event report (PADER), and also highlighted in the Institute for Safe Medication Practices (ISMP) QuarterWatch Report. Additionally, a FAERS data mining analysis by the Division of Applied Regulatory Science (DARS) suggested risks of autonomic dysfunction, falls and insomnia with pimavanserin. DPP opened a Tracked Safety Issue (TSI) to address these concerns. This review evaluates the safety profile of pimavanserin using a surveillance summary approach.

To inform potential regulatory action, DPV and the Divisions of Epidemiology (DEPI) I and II analyzed the following:

- FAERS data
- Clinical safety findings from the new drug application (NDA) review
- DARS review
- Thorough QT (TQT) study results
- Sponsor's PADER
- Sponsor's responses to the FDA's information requests (IR) for
    - additional information on and analysis of the postmarketing adverse event (AE) reports, especially the AEs involving or leading to death
    - clarification on the mortality rate calculation
    - drug utilization data
- Relevant published medical literature on Parkinson's disease (PD), Parkinson's disease psychosis (PDP), and the use of antipsychotics in PD and dementia

1.1. BACKGROUND

Media Attention

The ISMP publishes the QuarterWatch Reports to provide their perspective on emerging drug risks using the publicly available FAERS reports as their primary source of data. On November 1, 2017, the ISMP published the QuarterWatch Report – Safety Signals for Two Novel Drugs,[1] which focused on early AE data for pimavanserin. The Report shared concerns for the high volumes of AEs of "Hallucination," "Confusional state," "Drug ineffective," and "Death." ISMP stated that pimavanserin was approved on limited scientific evidence of its benefits. It also noted a safety concern of concomitant use with antipsychotics, which are not recommended for use in the elderly (see antipsychotics class Boxed Warning in **Section 1.3**), and are not approved for use in patients with PD. Furthermore, ISMP noted that this subset of patients were each taking a median of 10 different drugs.

On April 9, 2018, the Cable News Network (CNN) published an article titled "FDA worried drug was risky; now reports of deaths spark concern."[2] This article reported stories and interviews from caregivers, physicians, medical researchers and other experts. In addition, the article summarized ISMP's QuarterWatch Report, and responses from the Sponsor and FDA.

Parkinson's disease (PD) and Parkinson's disease psychosis (PDP)

PD is a progressive neurodegenerative disease that begins between 45 and 70 years of age, with the peak age of onset in the 60s. PD affects approximately 1 million people in North America.[3,4] Core features of PD include hypokinesia, bradykinesia, resting tremor, postural instability, and rigidity.[3] Progression of PD is characterized by worsening of motor features, and advanced stage disease is also associated with treatment-resistant motor features including gait and balance problems, and dysphagia.[5,6]

The mortality rate in PD is greater than that of many common life-threatening diseases in the elderly. In a large retrospective cohort study of Medicare patients, 64% of patients with PD died during the 6-year study period.[7] Dementia was the strongest risk factor for mortality in patients with PD.[7] The mortality rate for patients with incident PD was comparable to those for incident diagnoses of acute myocardial infarction (MI), hip fracture, and Alzheimer's disease. The PD adjusted mortality rate was higher than in patients with incident colorectal cancer, cerebrovascular accident (CVA), ischemic heart disease, and chronic obstructive pulmonary disease (COPD). The most common reasons for hospitalization in patients with terminal PD were infection, cardiovascular disease, and noninfectious pulmonary disease. Another retrospective cohort study using an administrative database demonstrated that patients with PD had a 43% greater risk of all-cause mortality compared to the general population of patients over the age of 65 years.[8] The most common causes of death for patients with PD were cardiovascular, neurologic, and respiratory disorders.

As the disease advances, psychosis can occur in 30 to 60% of drug-treated patients with PD.[6,9,10] PDP is a serious, highly disabling, late complication of treated PD, usually occurring 10 or more years after the initial diagnosis of PD.[11] The onset of PDP typically signals a malignant disease course and poor prognosis.[12] Risk factors associated with the onset of psychosis in PD include dementia, older age, longer duration of PD disease, more severe motor, axial and visual impairment, depression, and sleep disturbance.[11] PDP is mainly characterized by the presence of visual hallucinations, often in the form of people (known or unknown), animals[13], insects, or inanimate objects; however, hallucinations can also involve auditory, tactile, gustatory, or cenesthetic (involving viscera) phenemona.[14] Psychosis causes severe distress to patients, families, and caregivers. Delusions in particular, often the most serious symptoms of PDP, can lead to dangerous, disorganized, and suicidal behavior.[9] Hallucinations and delusions are frequently the reasons for nursing home placement, more commonly than either dementia or severe motor impairment.[9]

In addition, PDP is associated with increased mortality especially in patients with dementia and nursing home placement.[15] The reported mean survival times for patients with PDP vary among studies published in the literature; the range appears to be 2 to 4 years after recognition of psychosis.[15] In one study of patients with PDP requiring antipsychotic treatment, 30% died during the 4-month study period.[16] The most common causes of death were pneumonia and other pulmonary disorders.[16] In another long-term study of patients with PDP, 25% were deceased at 2 years, 42% were in nursing homes, and 68% had a diagnosis of dementia.[14] The most common cause of death in the study was pneumonia, followed by urosepsis, stroke, MI, and COPD. A

long-term observational study in patients with PD demonstrated that the presence of dementia increased the mortality risk more than 2-fold.[17]

Treatment options for PDP included dose reduction of antiparkinson/dopaminergic therapy (if contributing to PDP) or addition of antipsychotics such as quetiapine or clozapine (serotonergic and dopaminergic antagonist).[18] These treatments may improve PDP symptoms, however, they can worsen motor symptoms. In addition, these antipsychotics are not FDA-approved for PDP. As discussed in the antipsychotic medication class boxed warning, controlled trials demonstrated that antipsychotics increase the risk of mortality in elderly patient with dementia-related psychosis and behavioral disturbances. In addition, there appears to be an association between antipsychotic use and mortality risk in patients with PD, as demonstrated by a retrospective matched-cohort study.[19] Antipsychotic use was associated with a greater than 2-fold hazard ratio of death compared with nonuse. The authors note that patients with PD have disease-related morbidities that may predispose them to or overlap with common antipsychotic-related adverse events (AEs), including falls, orthostatic hypotension, parkinsonism, and sedation.[19]

Pimavanserin was the first atypical antipsychotic drug approved by FDA for the treatment of hallucinations and delusions associated with PDP in April 2016. Pimavanserin acts as a selective serotonin 5-HT_{2A} receptor inverse agonist and antagonist. Unlike other atypical antipsychotics, pimavanserin does not have activity at dopaminergic receptors, including D_2.[20] Pimavanserin is approved in the U.S. only.

1.2. Regulatory History

FDA approved pimavanserin for the treatment of hallucinations and delusions associated with PDP under the NDA 207318 on April 29, 2016. Pimavanserin is available as 17 mg oral tablets, and the recommended dosage is 34 mg once daily without titration. Pimavanserin is the only drug product indicated for the treatment of PDP. Drugs used off-label for the treatment of PDP include clozapine, quetiapine, and other antipsychotics.

1.2.1 Clinical Safety Findings from the NDA Review[21]

The approval of pimavanserin was based on a single placebo-controlled trial demonstrating efficacy in subjects with PDP. Accompanying data included results from three placebo-controlled pimavanserin trials that did not demonstrate efficacy, as well as two uncontrolled, long-term extension studies of pimavanserin in patients with PDP. In the clinical program, 616 patients with PDP had been exposed to pimavanserin at the time of data lock for the original NDA submission. Paul Andreason, M.D., Clinical Reviewer in DPP performed the NDA clinical review.

Common AEs in the Pimavanserin Trials

In the placebo-controlled trials, the most common AEs (occurring more frequently in the pimavanserin group compared to the placebo group) were peripheral edema (7% vs. 2%), confusional state (6% vs. 3%), hallucinations (5% vs. 3%), gait disturbance (2% vs. < 1%), nausea (7% vs. 4%), and constipation (4% vs. 3%). The types of hallucinations included visual, auditory, tactile, and somatic. A higher proportion of subjects in the pimavanserin group discontinued from the study because of AEs, compared with the placebo group (8% vs. 4%).

The AEs associated with discontinuation that were more common in the pimavanserin group were hallucination (2% vs. < 1%), urinary tract infection (1% vs. < 1%), and fatigue (1% vs. 0).

Deaths and Serious Adverse Events (SAEs) in the Pimavanserin Studies

In the 6-week, placebo-controlled trial population of the pimavanserin clinical program, there was an increased risk of SAEs, including death, in the pimavanserin group, compared to the placebo group. SAEs occurred in 7.9% of the pimavanserin group and 3.5% of the placebo group. In the NDA clinical review, Dr. Andreason concluded that the observed risk for SAEs in the pimavanserin 34 mg group (compared to the placebo group) was 2.38 (95% CI 1.00 to 5.73, p= 0.05).[21] For the lower dose pimavanserin (< 34 mg) group, the apparent elevated odds ratio for SAEs compared to placebo was not statistically significant [1.44 (95% CI 0.54 to 3.81, p=0.46)]. Dr. Andreason noted that there was no individual type of SAE that predominated. There appeared to be no unifying pathological mechanism or premonitory signal. Only three of 16 SAEs were viewed as "possibly drug-related" during the trials; these were psychiatric AEs. The remaining 13 of 16 SAEs were deaths and serious medical events, which were considered unrelated or unlikely to pimavanserin. Deaths occurred in four of 383 (1%) subjects in the pimavanserin group and one of 231 (0.4%) of the placebo group during the controlled trials. During the placebo-controlled trials, the causes of death in the pimavanserin group were: sepsis (n=1), septic shock (n=1), probable MI (n=1), and respiratory distress (n=1); the cause of death in the placebo group was respiratory arrest (n=1).

In the long-term PDP open-label studies with a wide duration of exposure (up to 8 years), there were 51 deaths (11.1%) among 459 subjects with PDP. The most common causes of death in the long-term open-label studies were: MI, aspiration pneumonia, pneumonia cardiac arrest, acute coronary syndrome, cardiorespiratory arrest, heart failure, sepsis, urosepsis, acute respiratory failure, CVA, and neoplasm. Dr. Andreason concluded that the types of deaths that occurred in the pimavanserin program did not appear to be pathologically uniquely different compared to what one might expect with the disease course of patients with PDP, a condition consistently associated with increased mortality.

QT Prolongation and Thorough QT (TQT) Study Results

Treatment with pimavanserin can cause significant QT prolongation. The Sponsor demonstrated a QT prolongation effect in a dedicated, moxifloxacin-controlled and placebo-controlled dedicated TQT study. As discussed in **Section 1.3**, the pimavanserin labeling includes a warning for QT prolongation. The design and results of the TQT study are discussed in more detail in **Section 3.3.2**.

1.2.2 DARS Consult Review[22]

DPV consulted DARS as part of a pilot project for identifying potential signals or risks based on data from new molecular entity NDAs. DPV and DARS selected pimavanserin for a predictive safety analysis, because it is a novel molecule for a new clinical indication. Keith Burkhart, M.D. performed the consult review.[22] The DARS team utilized several data sources including: a data mining bioinformatics tool (EFFECT), spontaneous reports from the FAERS database (and disproportionality analysis), and mechanistic data regarding a drug comparator. The purpose of

the analysis was to identify potential postmarketing events for further evaluation. Pimavanserin is a serotonin 5-HT_{2A} and 5-HT_{2C} inverse agonist. Unlike most antipsychotic drugs, pimavanserin does not demonstrate activity on dopamine D_2 receptors. The analysis used cyproheptadine as the best comparator drug, based on cyproheptadine's and pimavanserin's known target and binding profiles.

The DARS team concluded that treatment with pimavanserin has the potential to aggravate autonomic dysfunction (primarily blood pressure [BP] lability), falls, and insomnia in some patients with PDP. They noted that patients with PD are known to have these comorbidities secondary to their underlying disease process. In the EFFECT tool, cyproheptadine has a signal for hypertension. Labeling for cyproheptadine discusses hypotension. In addition, for pimavanserin, there were 12 FAERS reports noting hypertension and 19 FAERS reports of hypotension. Dr. Burkhart noted that serotonin regulation of BP is complex, "including bradycardia, tachycardia, hypotension, hypertension, and vasodilation or vasoconstriction." In animal models, there is a triphasic response to serotonin infusion, in which a transient depressor phase is followed by a pressor phase, subsequently followed by a prolonged hypotensive phase. Dr. Burkhart stated that in a patient population predisposed to BP lability, it is possible that altered serotonin neurotransmission by pimavanserin could potentiate and exacerbate hemodynamic fluctuations.

The analysis did not identify thrombotic events as expected AEs, which DPV inquired about based on the potential for serotonergic effects on platelet function.

1.3. PIMAVANSERIN PRODUCT LABELING[20]

BOXED WARNING – Increased Mortality in Elderly Patients with Dementia-related Psychosis

Labeling for all antipsychotic products includes a boxed warning regarding the increased risk of death in elderly patients with dementia-related psychosis. The warning is based on consistent findings from 17 short-term placebo-controlled antipsychotic trials for the treatment of psychosis and agitation in patients with dementia. The boxed warning for pimavanserin and the full text of the class warning are presented below.

> **WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**
>
> **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis *[see Warnings and Precautions (5.1)]*.**

WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Antipsychotic drugs increase the all-cause risk of death in elderly patients with dementia-related psychosis. Analyses of 17 dementia-related psychosis placebo-controlled trials (modal duration of 10 weeks and largely in patients taking atypical antipsychotic drugs) revealed a risk of death in the drug-treated patients of between 1.6- to 1.7-times that in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Nuplazid is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis [see Boxed Warning].

5.2 QT Interval Prolongation

Nuplazid prolongs the QT interval. The use of Nuplazid should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin, moxifloxacin) [see Drug Interactions (7.1)]. Nuplazid should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes (TdP) and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval [see Clinical Pharmacology (12.2)].

Reviewer's Comment: Pimavanserin causes significant QT prolongation, as demonstrated by a placebo-controlled, and active-controlled (moxifloxacin) dedicated thorough QT study. Details about the QT study and results are discussed below in Section 3.3.2.

DRUG INTERACTION

7.1 Drugs Having Clinically Important Interactions with NUPLAZID

Table 2 Clinically Important Drug Interactions with NUPLAZID QT Interval Prolongation	
Clinical Impact	Concomitant use of drugs that prolong the QT interval may add to the QT effects of NUPLAZID and increase the risk of cardiac arrhythmia.
Intervention	Avoid the use of NUPLAZID in combination with other drugs known to prolong QT interval *[see Warnings and Precautions (5.2)]*
Examples	Class 1A antiarrhythmics: quinidine, procainamide, disopyramide; Class 3 antiarrhythmics: amiodarone, sotalol; Antipsychotics: ziprasidone, chlorpromazine, thioridazine; Antibiotics: gatifloxacin, moxifloxacin

PHARMACCODYNAMICS – Cardiac Electrophysiology

12.2 Cardiac Electrophysiology

The effect of Nuplazid on the QTc interval was evaluated in a randomized placebo- and positive-controlled double-blind, multiple-dose parallel thorough QTc study in 252 healthy subjects. A central tendency analysis of the QTc data at steady-state demonstrated that the maximum mean change from baseline (upper bound of the two-sided 90% CI) was 13.5 (16.6) msec at a dose of twice the therapeutic dose. A pharmacokinetic-pharmacodynamic analysis with Nuplazid suggested a concentration-dependent QTc interval prolongation in the therapeutic range.

In the 6-week, placebo-controlled effectiveness studies, mean increases in QTc interval of ~5-8 msec were observed in patients receiving once-daily doses of Nuplazid 34 mg. These data are consistent with the profile observed in a thorough QT study in healthy subjects. Sporadic QTcF values ≥ 500 msec and change from baseline values ≥ 60 msec were observed in subjects treated with Nuplazid 34 mg; although the incidence was generally similar for Nuplazid and placebo groups. There were no reports of TdP or any differences from placebo in the incidence of other adverse reactions associated with delayed ventricular repolarization in studies of Nuplazid, including those patients with hallucinations and delusions associated with PDP [see Warnings and Precautions (5.2)].

2. METHODS AND MATERIALS

2.1. FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 2.1.1**. See **Appendix B** for further details on additional FAERS search strategies.

Table 2.1.1. FAERS Search Strategy*	
Date of Search	March 5, 2018
Time of Search	All reports through March 4, 2018
Search Type	FBIS Product-Manufacturer Reporting Summary
Product Terms	Product Active Ingredients: Pimavanserin, Pimavanserin tartrate
MedDRA Search Terms (Version 20.1)	All
Other criteria	Serious Outcome†

* See **Appendix A** for a description of the FAERS database.
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events.
Definitions: FBIS=FDA Business Intelligence Solution; MedDRA=Medical Dictionary for Regulatory Activity

2.2. DRUG UTILIZATION

2.2.1 Data Sources Used

Nuplazid is distributed exclusively to mail-order/specialty pharmacies (CVS, ACS, Walgreens, Accredo), specialty distributors (McKesson, AmeriscourceBergen, Cardinal, HD Smith), and is available under the Sponsor's free trial or patient assistance program (PAP), and as samples from physician offices.
As a result of this limited distribution, the proprietary drug utilization databases available to the FDA showed an incomplete capture of utilization. Therefore, an IR was sent to the Sponsor for utilization data.

The Sponsor provided FDA with the total number of tablets sold and unique patients who received a prescription for Nuplazid from U.S. mail-order and specialty pharmacies. specialty distributors, and physician offices for the aggregate time from June 2016 through March 2018. The data are stratified by patient age groups from 0-80 years in 10-year increments and 80+ years. **The drug sales and utilization data provided by the Sponsor are confidential and for internal FDA purposes only; this information cannot be released or discussed publicly without the Sponsor's approval.**

2.3. OTHER DATA SOURCES

2.3.1. Periodic Safety Reports

DPV reviewed the Periodic Adverse Drug Experience Report (PADER) No.7, October 29, 2017 to January 28, 2018.

2.3.2. Thorough QT Study

As part of the original NDA submission, the Sponsor was required to conduct a dedicated TQT study. The Sponsor conducted Protocol Number ACP-103-018 under NDA 207318. The FDA Interdisciplinary Review Team for QT Studies (QT-IRT) reviewed the study results. Dr. Li Zhang filed the QT-IRT review on October 27, 2015.

2.3.3. The Sponsor's Information Request (IR) Responses

On April 13, 2018, the Sponsor submitted a response to FDA's IR dated March 19, 2018. The FDA requested additional information on postmarketing AEs reports for pimavanserin.[23] Specifically, the FDA requested an analysis regarding AEs involving or leading to death, including:

- Cause of death
- Date of event or death
- Time to onset
- Concomitant medications (including therapy dates)
- Electrocardiogram (ECG) and laboratory results (if available)
- Physical examination (if available), and
- Any other relevant clinical information

The purpose of this IR was to attempt to better characterize fatal AE reports, and identify any clinical trends indicative of a causal relationship between fatal AEs and pimavanserin.

The Sponsor submitted an additional IR response on April 19, 2018,[24] which addressed questions FDA had regarding how the Sponsor calculated the mortality per 100 years in controlled trials submitted in the previous IR response.

The Sponsor included an update on mortality in controlled trials in an IR response on May 10, 2018.[25]

3. RESULTS

3.1. FAERS CASE SELECTION

The FAERS search retrieved 2,209 reports with serious outcomes (**Table 3.1.1**). For the purpose of this review, a detailed case-level review was not performed on all 2,209 reports. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.), miscoded reports, or unrelated reports. Reported outcomes for this section are the coded outcomes submitted to FDA; causality and the role of the product in the coded outcome have not been determined for all reports (see **Appendix A** for FAERS limitations).

We focused on cases reporting death, TdP/QT prolongation, other events of interest (e.g., seizure, CVA), off-label use, and use in patients <65 years of age in **Sections 3.1.2**, **3.1.3**, **3.1.4**, **3.1.5** and **3.1.6**, respectively.

Table 3.1.1. Descriptive Characteristics of FAERS Reports for Pimavanserin, Received by FDA through March 4, 2018
N=2,209*

Sex	Male	1,287
	Female	672
	Not reported	250
Age	<1 to <17 years	0
	17 to <65 years	96
	>= 65 years	1,275
	Not reported	838
Country	United States	2,209
Report Type	Expedited	2,058
	Direct	94
	Periodic	57
Serious Outcomes (n=2,209)†	Death	896
	Life-threatening	10
	Hospitalization	1,069
	Disability	14
	Other serious	629

* May include duplicates
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. Each report may report more than one serious outcome.

3.1.1. Most Frequently Reported MedDRA Preferred Terms (PTs)

Table 3.1.1.1. Top 50 Most Frequently Reported MedDRA PTs for Pimavanserin, Received by FDA through March 4, 2018, Sorted by Decreasing Number of FAERS Reports per PT

Row	MedDRA PT	Number of FAERS Reports*	Labeled (Yes/No), Location or Other Category†
1.	Death	614	Yes, BW and AR. See **Section 3.1.2**.
2.	Hallucination	362	Yes, AR and IR
3.	Nonspecific reaction	186	No, U
4.	Fall	185	No, DR
5.	Confusional state	173	Yes, AR
6.	Drug ineffective	130	No, U
7.	Gait inability	124	Yes, AR (Gait disturbance)
8.	Parkinson's disease	114	IR
9.	Pneumonia	113	Yes, BW
10.	Urinary tract infection	110	Yes, AR
11.	Drug dose omission	98	No, U
12.	Off label use	93	No. See **Section 3.1.3**.
13.	Prescribed underdose	93	No, U
14.	Asthenia	81	No, DR
15.	Somnolence	81	Yes, AR
16.	Aggression	79	No, DR
17.	Delusion	79	IR
18.	Abnormal behaviour	76	No, U
19.	Gait disturbance	74	Yes, AR
20.	Hospitalisation	71	No, U
21.	Agitation	62	No, DR
22.	Insomnia	57	No, DR
23.	Dysphagia	54	No, DR
24.	Dementia	50	No, DR
25.	Dehydration	49	No, DR
26.	Dysstasia	49	No, DR
27.	Nausea	48	Yes, AR
28.	Decreased appetite	47	No, DR
29.	Unresponsive to stimuli	46	Yes, AR (Somnolence)
30.	Feeling abnormal	45	No, U
31.	Peripheral swelling	44	Yes, AR
32.	Fatigue	42	Yes, AR
33.	Constipation	40	Yes, AR
34.	Balance disorder	39	Yes, AR (Gait disturbance) and DR

Table 3.1.1.1. Top 50 Most Frequently Reported MedDRA PTs for Pimavanserin, Received by FDA through March 4, 2018, Sorted by Decreasing Number of FAERS Reports per PT

Row	MedDRA PT	Number of FAERS Reports*	Labeled (Yes/No), Location or Other Category†
35.	Dizziness	39	No, CM
36.	Psychotic disorder	39	No, DR
37.	Lethargy	38	Yes, AR (Somnolence)
38.	General physical health deterioration	37	No, DR
39.	Inappropriate schedule of drug administration	37	No, U
40.	Tremor	37	No, DR
41.	Paranoia	36	No, DR
42.	Seizure	36	No. See **Section 3.1.4.**
43.	Weight decreased	36	No, DR
44.	Anxiety	34	No, DR
45.	Cerebrovascular accident	34	No. See **Section 3.1.4.**
46.	Malaise	34	Yes, AR
47.	Loss of consciousness	33	No. See **Section 3.1.3.**
48.	Hip fracture	32	No, DR
49.	Myocardial infarction	31	No. See **Section 3.1.4.**
50.	Underdose	31	No, U

* A report may contain more than one MedDRA PT.
† Definitions: BW=Box Warning; W/P=Warnings/Precautions; AR=Adverse Reactions; PCI=Patient Counseling Information; DR=Disease-related; IR=Indication-related; U=Uninformative; CM= Confounded by concomitant medications

The majority of the reported drug-event combinations were consistent with the known risks described in the labeling such as death, confusional state, gait inability/disturbance, and pneumonia, or disease related such as fall, asthenia, and dysphagia. Although increased mortality in the elderly is labeled as a part of the class Boxed Warning, we further evaluated all fatal reports in Section 3.1.2.

3.1.2. Death

The FAERS search retrieved 896 fatal reports. See **Appendix B Table 8.2.1** for the FAERS search strategy for the fatal reports. After accounting for duplicates (3), we included an analysis of the remaining 893 cases in this section. See **Appendix C** for a line listing of the 893 fatal cases. See **Section 3.1.3** for further details on cardiovascular events including QT prolongation.

Table 3.1.2.1 summarizes the 893 fatal FAERS cases (categorized by solicited cases and non-solicited cases). We considered FAERS cases as solicited cases if they were reported via specialty pharmacies or Nuplazid Connect, a patient support program for pimavanserin.

Table 3.1.2.1. Descriptive Characteristics of Fatal FAERS Cases for Pimavanserin, Received by FDA through March 4, 2018

(N=893)

	Solicited Cases (n=657)	**Non-Solicited Cases (n=236)**
Sex		
Male	452	155
Female	204	78
Not reported	1	3
Age (years)	(n=643)	(n=225)
Mean	78	78
Range	47-97	54-89
Reasons for Use		
PDP	365	154
PD, NOS	263	53
PD with dementia	1	1
Dementia/Alzheimer's	7	10
Others*	7	3
Not reported	14	15
Duration of therapy	1 day – 19 months (n=483)	1 day – 31 months (n=170)
Time to death from initiation	(n=486) 10 days – 19 months	(n=179) 2 days – 31 months
Hospice care or advanced PD	92	46
Long term care facility	45	28
Causes of death†		
Not reported	490	157
PD	61	23
Underlying disease/Natural cause	25	0
Pneumonia	23	21
Dementia	18	5
MI/Heart attack	11	5
Respiratory failure/arrest	11	6
Cardiac Failure/CHF	7	6
Sepsis/septic shock	7	4
Cancer	6	4
Cardiac arrest	6	5
CVA	5	2
Fall	4	3
Failure to thrive	3	1
Others	14‡	8§
Concomitant medications		
Reported	283	150
Not reported	374	86
Concomitant antipsychotics†	(n=93)	(n=54)
Quetiapine	77‖	47‖
Risperidone	6	1

Table 3.1.2.1. Descriptive Characteristics of Fatal FAERS Cases for Pimavanserin, Received by FDA through March 4, 2018

(N=893)

	Solicited Cases (n=657)	Non-Solicited Cases (n=236)
Haloperidol	6	3
Olanzapine	4[I]	2
Clozapine	2[I]	3
Aripiprazole	1[I]	2
Ziprasidone	1	1
Trifluoperazine	0	1

* Include psychotic disorder NOS, muscle weakness, torticollis, leukemia, progressive supernuclear palsy

† Each case may report more than one

‡ Include cardiac disorder NOS (2), liver cirrhosis/failure (2), COPD (2), internal bleeding (2), blood clot NOS (1), choking (1), hypothermia (1), paradoxical reaction (1), renal injury (1), and UTI (1)

§ Include DVT/PE (2), suicide (2), aortic dissection (1), blood clot NOS (1), organ failure NOS (2), neuroleptic malignant syndrome (1), perforated bowel (1), post-operative complication (1), renal failure (1), and UTI (1)

I Include cases described stopping the antipsychotic when pimavanserin was started [quetiapine (1 solicited reports, 1 non-solicited reports), olanzapine (1), clozapine (1), aripiprazole (1)]

Definitions: MI=Myocardial infarction; CHF=Congestive heart failure; CVA=Cerebrovascular accident; COPD=Chronic obstructive pulmonary disease; DVT=Deep vein thrombosis; NOS=Not otherwise specified; PD=Parkinson's disease; PDP=Parkinson's disease psychosis; PE=Pulmonary embolism; UTI=Urinary tract infection

The majority of fatal cases were solicited cases from Nuplazid Connect or specialty pharmacies, and these cases generally did not provide enough information to assess drug-event causality. In both solicited and non-solicited cases, most patients were male with age ranging from 47 to 97 years. The most commonly reported reasons for use were PDP and PD, NOS. Patients were under hospice care or reported to have advanced/end stage PD in 140 cases [solicited (95) and non-solicited (45)]. Fatal cases reported a wide range of time-to-death after beginning treatment with pimavanserin, ranging from days to years, and taking multiple concomitant medications including antipsychotics. Among 147 cases that reported concomitant antipsychotic use, 124 cases reported use of quetiapine. Most cases did not provide a cause of death or enough clinical details for assessing any potential contributory role of pimavanserin. Among cases that provided the causes of death, the most commonly reported causes were PD progression/complication followed by "underlying disease"/ "natural cause," then pneumonia. Three cases reported autopsy results, which stated the following reasons for death: 1) "PD related;" 2) Lewy body disease, aspiration pneumonia and cardiomegaly; and 3) cardiac arrest due to coronary artery disease (CAD), hypertension, 60% restriction in the artery and peripheral arterial disease. One case coded with a fatal outcome reported "possible brain death" in a patient under palliative care after being found unresponsive on the floor and developed a pulmonary embolus (PE) while in hospital. This case did not provide further information.

We summarized two fatal cases with autopsy results and one case with limited clinical information from the case series. (See **Section 3.1.3** for the third case with autopsy results):

FAERS Case #13253411, Version 3, Expedited, Non-Solicited:
A 75-year-old male patient with PD for more than 16 years, dysphagia, and deep brain stimulator started pimavanserin for PDP. Concomitant medications included clonazepam, ibuprofen and

carbidopa/levodopa. The patient lived in a nursing home and his "state of health was poor." Five months after initiation of pimavanserin, the patient experienced dyspnea and fever, and was hospitalized for pneumonia. Four days later, the patient passed away due to pneumonia. The autopsy results stated that the cause of death was "PD related." This case did not provide any further information.

Reviewer's Comment:
This case described an elderly patient who died from pneumonia after receiving pimavanserin for five months. The patient had advanced age, long-term PD with dysphasia, and poor state of health. The most common consequences of dysphagia from PD is aspiration and pneumonia.[26] *The patient had underlying risk of pneumonia and the autopsy results showed the death was related to PD. Due to lack of clinical details and several underlying risk factors, we were not able to determine the role of pimavanserin in pneumonia and death.*

FAERS Case #13097147, Version 2, Expedited, Non-Solicited
A 72-year-old male patient with PD, dementia, and orthostatic hypotension started pimavanserin for PD, NOS. Concomitant medications included clonazepam, fludrocortisone, pravastatin, metformin, glipizide, finasteride, oxybutynin and carbidopa/levodopa. On an unspecified date (same year pimavanserin was initiated), the patient passed away. The patient had encephalopathy delirium prior to death and the autopsy results showed Lewy body disease, aspiration pneumonia and cardiomegaly. This case did not provide any further information.

Reviewer's Comment:
This case described an elderly patient who died from Lewy body disease, aspiration pneumonia and cardiomegaly after receiving pimavanserin for an unknown period of time. The patient had advanced age, multiple comorbidities and multiple concomitant medications. Due to lack of clinical details and several underlying risk factors, we were not able to determine the role of pimavanserin in pneumonia and death.

FAERS Case #13880412, Version 3, Expedited, Solicited
A 46-year-old male was hospitalized for an unspecified reason six months after initiating pimavanserin 34 mg once daily for PD. The patient had "spiked fevers" and had "shakes" while hospitalized, and passed away from "complication of illness" (unspecified) 113 days from date of hospitalization. Despite three follow-up attempts by the Sponsor, limited additional clinical information was obtained.

Reviewer's Comment:
This case described a PD patient who died from unspecified "complication of illness." Due to lack of clinical details, we were not able to determine the role of pimavanserin in "complication of illness" and death.

3.1.3. Cardiovascular Events, TdP, and QT Prolongation FAERS Cases

We searched the FAERS database to capture deaths and other serious cardiovascular events potentially related to pimavanserin and QT prolongation. Refer to **Appendix B Table 8.2.2** for further details on the FAERS search strategy for these cases. **Table 3.1.3.1** presents all of the

Preferred Terms (PTs) in the Torsade de Pointes/QT Prolongation Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) and the number of unique FAERS cases retrieved in the search for each term. The search captured 91 FAERS reports, including duplicates (3), for a total of 88 unique patient cases. See **Appendix D** for a line listing of the 88 cases. There were 83 SAE cases and 5 non-SAE cases. The most common PTs captured by the search were: *Loss of consciousness* (n=34), *Electrocardiogram QT prolonged* (23), *Cardiac arrest* (15), and *Syncope* (13). There were no cases reporting TdP or any type of ventricular arrhythmia. A higher proportion of cases were solicited (67%) than reported spontaneously (33%).

Table 3.1.3.1. Reported MedDRA PTs in Torsade de Pointes/QT Prolongation SMQ (Broad) for Pimavanserin, Received by FDA through March 4, 2018

MedDRA PTs in SMQ	Total Number FAERS Cases N=88 (Fatal=25)	Solicited Cases N=58 (Fatal=15)	Non-Solicited Cases N=30 (Fatal=10)
Loss of Consciousness	32 (3)	25 (2)	7 (1)
Electrocardiogram QT prolonged	23	14	9
Cardiac Arrest	15 (14)	8 (8)	7 (6)
Syncope	13 (3)	7 (1)	6 (2)
Cardio-respiratory Arrest	3 (3)	2 (2)	1 (1)
Sudden cardiac death	1 (1)	1 (1)	0
Sudden death	1 (1)	1 (1)	0

Generally, the patients with PDP in these cases had advanced Parkinson's disease and were elderly. The mean age was 80.4 years, and the age range was 54 to 92 years. Patients commonly had numerous medical comorbidities that are significant risk factors for death and SAEs. These included: cardiovascular disease (e.g., CAD, MI, congestive heart failure, PE, abdominal aortic aneurysm [AAA], atrial fibrillation), cerebrovascular disease, dementia, chronic pulmonary disease, diabetes mellitus, chronic kidney disease, neurogenic orthostatic hypotension, autonomic instability, neoplasms, and serious infection (e.g., pneumonia, urosepsis). Many patients were treated concomitantly with antipsychotics (e.g., quetiapine) or antidepressants (e.g., escitalopram, fluoxetine) that can prolong the QT interval. Numerous patients were concomitantly treated with diuretics, which can cause electrolyte disturbances and increase the risk of QT prolongation. Furthermore, antipsychotic treatment may increase the risk of all-cause mortality in patients with PD and elderly patients with dementia.

A high proportion of these FAERS cases had limited information regarding the specific AEs, potential temporal relationships between pimavanserin treatment and AEs, medical history and risk factors, concomitant medications, and clear documentation of actual exposure to pimavanserin. Several solicited cases either confirmed that patients had not actually begun treatment with pimavanserin, or there was uncertainty about whether the patient had begun treatment. Only one case reported autopsy results to confirm a cause of death; additional details of this case are provided in **Section 3.1.3.1**. Thus, most cases were difficult to interpret and

confirm or rule out a causal relationship with pimavanserin. Moreover, because many of the potential cardiovascular events and deaths were unwitnessed and not monitored with ECG, it was difficult to adjudicate events. In addition, potential syncopal events and loss of consciousness (LOC) events are typically difficult to diagnose initially, and often require detailed further investigation for attributing a causal mechanism.

There were 25 deaths captured under the following PTs in the relevant SMQ: *Cardiac arrest* (14), *Cardiopulmonary arrest* (3), *Sudden cardiac death* (1), and *Sudden death* (1). Six fatal cases were captured under the PTs *Loss of consciousness* (3) and *Syncope* (3); the probable causes of death in these cases were: esophageal cancer (1), PE (1), pneumonia (1), stroke (1), CVA and seizure (1), CVA and pneumonia (1). None of the fatal cases reported TdP, other ventricular arrhythmia, or QT prolongation. In some fatal cases, the patients were found deceased after unknown periods during which they were not observed. There was one case reporting pulseless electrical activity (PEA) in a patient with a history of AAA, possibly consistent with a dissecting AAA. In other fatal cases, likely causes of death or major contributing factors included: MI, PE, vena cava thrombosis, congestive heart failure, CVA, esophageal cancer, pneumonia, end-stage renal failure and death during dialysis, and possible post-surgical complications after hip fracture.

3.1.3.1. Representative FAERS Cases of Sudden Death or Cardiac Arrest

FAERS Case #13814966, Version 2, Expedited, Solicited (Nuplazid Connect)
PTs *Sudden cardiac death, Nausea, Dizziness, Hallucination, Hypersomnia*
The information was provided by the patient's daughter. The patient was an 81-year-old female with a diagnosis of PDP, with hallucinations and delusions for about two years. The patient had a hip fracture and surgery four weeks previously. Concomitant medications included quetiapine, escitalopram, carbidopa/levodopa, and aspirin. There was no other reported medical history. On Day 1, the patient began treatment with pimavanserin 34 mg daily. The following day (Day 2 of treatment), the patient awoke with severe nausea. The daughter also noted that "she did sleep a lot that night before and did not feel well." The patient died suddenly on Day 2 in her home. It is not clear whether she had taken a second pimavanserin dose. The daughter stated that the death was sudden and unexpected and that her mother was not ill. She reported that the physicians "think that it could have been a sudden heart issue," but an autopsy was not performed. The family thought the death and other AEs were possibly related to pimavanserin. There was no other clinical information provided.

Reviewer's Comment: This appears to be a well-documented case of sudden death. Although there were no confirmatory ECG data or autopsy data, it appears likely that this was a primary cardiac event; there was no reported evidence of significant non-cardiac disease, and the patient was elderly. However, there is considerable missing information about whether the patient had risk factors such as previously diagnosed or undiagnosed cardiovascular disease, arrhythmia, pulmonary, or other disease. The events could be consistent with a serious cardiac event related to QT prolongation. The patient was treated with three medications that can prolong the QT interval: pimavanserin, quetiapine, and escitalopram. Although not apparently diagnosed or treated for CHD (a risk factor for sudden cardiac death), the patient was elderly, had PDP, and possibly had significant underlying disease such as CAD, hypertension, etc.

FAERS Case #13868124, Version 2, Expedited, Solicited (Nuplazid Connect)
PTs *Sudden death, Somnolence*
The information was provided by the patient's husband and daughter. The patient was a 76-year-old female with a diagnosis of PDP with hallucinations and delusions. She started pimavanserin 34 mg daily and was treated for approximately five months. Throughout treatment, the patient reported excessive sedation ("need to nap and feel very groggy"). On an unknown date after discontinuing pimavanserin, the patient reportedly went to the hospital for a routine visit but was quickly admitted to an intensive care unit and died. The patient's daughter reported that "it was a sudden passing." There were no other details regarding past medical history, concomitant medications, hospital course, or other AEs. There was no reported autopsy or stated cause of death.

Reviewer's Comment: Important clinical information was missing regarding specific AEs, past cardiac or other medical history, and concomitant medications that could have been risk factors for the death. It was not possible to confirm or rule out a causal role for pimavanserin. However, it seems unlikely that pimavanserin contributed to the death, because of the long latency after beginning pimavanserin, and pimavanserin was discontinued before the fatal events.

FAERS Case #12507321, Version 3, Expedited, Non-Solicited
PTs *Cardiac arrest, Arrhythmia, Coronary artery occlusion, Hypertension, Hypertensive angiopathy, Peripheral arterial occlusive disease, Somnolence*
The information was provided by the patient's family and physician. The patient was a 73-year-old female in a long-term care facility, with PDP with hallucinations and delusions, dementia, hypertension, orthostatic hypotension, colitis, urinary incontinence, and gastroparesis. Concomitant medications included domperidone, carbidopa/levodopa, aspirin, ramipril, valproate, midodrine, polyethylene glycol (PEG) 3350, galantamine, and levothyroxine. The patient began treatment with pimavanserin 34 mg daily on either Day 1 or Day 2 (there are conflicting reports). The dose was decreased to 17 mg on Day 2 or Day 3. On Day 4 at 7:55 AM, the patient was ambulating but reported feeling sedated. Later in the morning, the patient was found unresponsive and pulseless, underwent cardiopulmonary resuscitation (CPR) and resuscitative efforts, and was pronounced dead at 8:34 AM. The autopsy report stated that the cause of death was primary cardiac arrest secondary to CAD. It was reported that the autopsy results further stated that the cause of death was "atherosclerotic and hypertensive cardiovascular disease with terminal/fatal arrhythmia," with 2-vessel disease, slight cardiomegaly, bi-ventricular dilatation, and left ventricular hypertrophy, consistent with sudden terminal fatal cardiac arrhythmia. The proximal left anterior descending (LAD) coronary artery had 80-90% occlusion, and the right coronary arteries had 60-70% occlusion. There was no recent or healing coronary artery thrombus, and the myocardium was homogenous, dark-red, and firm without pallor, hemorrhagic infarction, or softening. There was no evidence of congestive heart failure, PE, or cerebral infarction. Neuropathology was consistent with idiopathic PD, with no evidence of Alzheimer's disease or Lewy body dementia.

Reviewer's Comment: Dr. Daniel Woronow, cardiologist in DPV, reviewed this case. Dr. Woronow concluded that it is possible that pimavanserin contributed to cardiac arrest and sudden death in this case, as suggested by the short time to onset of events (2-4 days) after

initiating pimavanserin and other features consistent with primary cardiac events. The immediate cause of death was likely a non-infarct related ventricular cardiac arrhythmia (although, there were no ECG data reported). The autopsy findings do not seem to demonstrate evidence of a significant MI related to the patient's death. The autopsy is consistent with pre-existing CAD and pre-existing left ventricular dysfunction, which are risk factors for fatal ventricular arrhythmia (i.e., sudden death). This patient had a "widow(er) maker" 80-90% stenosis of the proximal LAD coronary artery. Concomitant medications included domperidone, which causes QT prolongation. In Canadian product labeling, domperidone has a Boxed Warning for serious ventricular arrhythmias or sudden cardiac death. In the U.S., domperidone is available under an investigational drug (IND) protocol only. The patient's death could have been related to her underlying heart disease, domperidone, pimavanserin, or a combination of these arrhythmia risk factors.

FAERS Case #12615218, Version 2, Expedited, Non-Solicited

PTs *Cardiac arrest, Pulseless electrical activity, Respiratory failure*

This was an 89-year-old female with a diagnosis of PDP with auditory and visual hallucinations. A physician provided follow-up information. The patient was treated with pimavanserin 34 mg daily for 10 or 11 days. Past medical history included CAD, abdominal aortic aneurysm (AAA), hypertension, pacemaker placement, atrial fibrillation, diabetes mellitus, asthma, COPD, hypothyroidism, gastroesophageal reflux disease (GERD). There were numerous concomitant medications including ondansetron, formoterol, digoxin, diltiazem, hydrocodone/acetaminophen, potassium, insulin, dofetilide, torsemide, warfarin, valsartan, prochlorperazine, and nebivolol. The patient had a witnessed arrest in a nursing home, and presented to the emergency room (ER) in cardiac arrest, found to have pulseless electrical activity (PEA) and wide complex tachycardia. The patient had full resuscitative efforts, including CPR, five doses of epinephrine, and intubation.

Reviewer's Comment: Dr. Woronow concluded that multiple medications and disease-related factors likely contributed to the patient's demise. There is no evidence that pimavanserin contributed directly to the patient's death; however, it is possible that pimavanserin could have contributed through QT-prolonging effects. Dofetilide is a TdP/QT prolonging drug. The combination of digoxin and dofetilide is concerning. The dofetilide labeling in the Potential Drug Interactions section states "the concomitant administration of digoxin with dofetilide was associated with a higher occurrence of Torsade de Pointes." However, "No increase in mortality was observed in patients taking digoxin as concomitant medication" (with dofetilide). The concomitant use of diltiazem and nebivolol may have additional pharmacodynamic effects, although these should be ameliorated by the patient's pacemaker. In general, pacemaker therapy may be somewhat protective against TdP. Ondansetron is also associated with TdP/QT prolongation. Formoterol has QT effects and has labeling for QT prolongation. The patient was on a torsemide diuretic and several potassium-affecting drugs, which could also contribute to TdP or other ventricular arrhythmias.

The patient's initial cardiac event was PEA. Electrical pacemaker activity in an asystolic patient can be mistaken for PEA. Medical history included AAA, which may have ruptured and caused undetected massive internal hemorrhage leading to PEA. A respiratory arrest and hypoxia may have preceded the PEA. PE leading to PEA is less likely in this warfarin-treated patient.

Apparently, the ER staff was able to obtain a wide complex tachycardia after multiple doses of epinephrine, which is a common sequela in this type of resuscitation attempt scenario.

This patient also had a history of CAD, as would be expected with the multiple risk factors and advanced age. MI is a common cause of death in such patients.

FAERS Case #14239437, Version 1, Expedited, Solicited (Nuplazid Connect)
PTs *Cardiac arrest, Circulatory collapse*
This was a 74-year-old female with PDP, hallucinations and delusions. The only past medical history provided was that the patient had been on dialysis during the fatal event. The report stated that the patient collapsed during dialysis, went into cardiac arrest, was taken to hospital, and died. The cause of death was reported as cardiac arrest. Prior to hospitalization, the patient was living at home. No additional information was reported. It could not be confirmed whether the patient had begun treatment with pimavanserin; the first medication shipment was reportedly received six days prior to the event, and the second was received on the day of the event.

Reviewer's Comment: It is difficult to assess the cause of death or potential role of pimavanserin, because of limited clinical information about the current and past medical history, medication history, and uncertainty about actual exposure to pimavanserin. It is not uncommon for dialysis patients to experience sudden cardiac arrest or circulatory collapse secondary to complications of end-stage renal failure and hemodialysis. The risk of sudden cardiac death is high in patients with chronic kidney disease.[27] The most common causes are ventricular tachycardia, ventricular tachyarrhythmia, TdP, sustained ventricular fibrillation, and bradyarrhythmia. Dialysis has important cardiovascular effects that can cause hemodynamic and electrolyte disturbances and affect myocardial electrophysiology. Dialysis can increase vulnerability to serious arrhythmia through sudden shifts in fluid status and electrolytes, particularly potassium and calcium.

As illustrated in the FAERS cases in Section 3.1.3.1, most of the sudden cardiac death (SCD) and sudden cardiac arrest (SCA) cases did not involve witnessed events, and no patients had ECG monitoring before the events occurred. Thus, it was not possible to determine the precise cause of death or determine whether pimavanserin had a causal role in the events. The causal mechanism(s) can only be inferred, based upon information obtained after the event; however, in these FAERS cases, clinical information was usually limited.

SCD is a common cause of death, accounting for approximately 15% of total mortality in the U.S.[28] The incidence of SCD and SCA increase dramatically with age and underlying cardiac disease. All patients in these SCD and SCA cases were elderly and had cardiovascular or other risk factors for sudden fatal events which included: CHD, AAA, hypertension, concomitant hemodialysis, treatment with QT interval-prolonging drugs, and advanced age. Most risk factors for CHD are also risk factors for SCA. SCA and SCD typically occur secondary to sustained ventricular tachycardia or ventricular fibrillation.[29] These events mostly occur in patients with structural cardiac disease, particularly coronary heart disease (CHD).[30] Approximately 65% to 70% of all SCDs are attributable to CHD. In several cases of SCD, it is possible that pimavanserin contributed to the fatal events, particularly if there was QT prolongation and ventricular arrhythmia; however, none of these cases involved ECG documentation of QT

prolongation. Furthermore, there are many cardiac and noncardiac causes for a sustained ventricular tachyarrhythmia that can result in sudden death; approximately 15% to 25% of cardiac arrests are noncardiac in origin.

3.1.3.2. Representative FAER Cases Reporting QT Interval Prolongation

FAERS Case #13136975, Version 1, Expedited, Non-Solicited
PTs *ECG QT prolonged, Bradycardia, Blood pressure decreased, Encephalopathy*
The information was provided by a medical technician, with follow-up from a physician. The patient was a 79-year-old male with PDP, treated with pimavanserin 34 mg daily. Concomitant medications included carbidopa/levodopa, oxybutynin, and PEG 3350. No other medical history was provided. The reporter stated that the "blood pressure was very low and patient was really out of it and pulse was 45." Pimavanserin was discontinued on Day 11 of treatment because of hypotension (75/55 mmHg). The patient's BP reportedly returned to baseline. The physician reported that the patient experienced bradycardia and encephalopathy, and the patient's condition improved on Day 11. The ECG reportedly demonstrated "sinus bradycardia with prolonged QT interval." There were no numerical ECG data or baseline ECG for comparison. The physician and technician considered the AEs related to pimavanserin.

Reviewer's Comment: There was limited clinical information available for this case. It is possible that pimavanserin contributed to encephalopathy. Pimavanserin is not known to cause hypotension; however, it is possible that pimavanserin could cause BP lability through its serotonergic effects. It is possible that pimavanserin caused QT prolongation in this case.

FAERS Case #13245830, Version 3, Expedited, Non-Solicited
PTs *ECG QT prolonged, Myocardial infarction, Palpitations, Chest pain, Confusional state*
The information was provided by the patient's daughter. The patient was an 85-year-old male with a diagnosis of PD, dementia, and possibly Lewy body disease, treated with pimavanserin 34 mg for approximately three months. Concomitant medications included escitalopram, spironolactone, propranolol, carbidopa/levodopa, aspirin, warfarin, ibuprofen, mirabegron, paroxetine, donepezil, and gabapentin. Several weeks after beginning pimavanserin, the patient experienced an increase in heart rate and chest pain. An ECG reportedly demonstrated QT prolongation; however, the reporter stated that it was uncertain whether this had existed prior to treatment with pimavanserin. No additional ECG data were reported. The physician decided to discontinue pimavanserin because of concern about QT prolongation. Approximately one to two months after discontinuing pimavanserin, the patient had an MI

Reviewer's Comment: The patient had several risk factors for QT prolongation, including pimavanserin, escitalopram, and donepezil. However, because of limited information, it is not clear that the patient had an increase in QT interval after beginning pimavanserin. It is possible that CHD and ischemia contributed to the events.

FAERS Case #13252867, Version 1, Non-Expedited, Non-Solicited
PTs Electrocardiogram QT prolonged, Delusion, Hallucination
The information was provided by a 78-year-old male patient with PDP, delusions, and memory impairment. A physician provided follow-up information. The patient stated that he "didn't like

the way his heart was functioning" during treatment with pimavanserin 34 mg daily. Significant medical history included congestive heart failure and dilated cardiomyopathy. The patient's concomitant medications included donepezil, memantine, and amantadine. The reported pre-pimavanserin QT interval was 342 ms. Approximately two weeks after beginning pimavanserin, the QT interval was 420 ms. Reportedly the patient's cardiologist concluded that the patient had QT prolongation, and discontinued pimavanserin.

Reviewer's Comment: It is possible that pimavanserin caused or contributed to QT interval prolongation. However, there were numerous additional risk factors for QT prolongation, including: donepezil, amantadine, and underlying heart disease (cardiomyopathy, heart failure, and possibly CHD).

There were 23 FAERS cases containing the PT *Electrocardiogram QT Prolongation*. None of these cases were fatal or involved documented TdP or other ventricular arrhythmia. Most reports were not clinically confirmed as actual cases of QT prolongation. Most reports had sparse information and did not include actual ECG data regarding a measured QT interval. Only one case reported a numerical QT value, and only one case referred to a baseline ECG before beginning treatment with pimavanserin. Most of the QT cases were solicited, in which a family member stated that the patient apparently had an episode of QT prolongation. In two solicited cases, family members expressed concern about the potential for QT prolongation with pimavanserin, but they did not state that the patient experienced QT prolongation.

In some cases, health care professionals reported that patients had experienced QT prolongation, but most did not include ECG data or make reference to a pre-treatment ECG. None of the cases reported symptoms that could be attributed to QT prolongation; and several clinicians specifically noted that patients were asymptomatic, and the ECGs were performed for non-specific reasons (e.g., routine scheduled ECGs, or for insurance purposes). In several cases, pimavanserin was continued because it was reportedly providing benefit; however, some cases reported discontinuation of pimavanserin or dose reduction because of QT prolongation.

There were numerous concomitant medications in the cases that could have contributed to drug-drug interactions and QT prolongation, through pharmacodynamic or pharmacokinetic effects. As noted, numerous patients were treated concomitantly with antipsychotics that can prolong the QT interval and have QT warnings: quetiapine, clozapine, asenapine, paliperidone, and iloperidone. Some were treated with the antidepressant, citalopram, which can cause QT prolongation. These drugs are not currently listed in the pimavanserin label. Several of these patients were also treated with diuretics, increasing the risk of electrolyte abnormalities, QT prolongation, and serious cardiovascular AEs. Many of these patients had treatment with supplemental potassium, probably indicating that they had a history of hypokalemia or were considered at significant risk of developing hypokalemia. Diuretic treatment is also a risk factor because of its correlation with heart failure, as well as direct blockade of potassium current by some diuretics.[31] Bradycardia is an additional risk factor for QT prolongation, which may be related to a fall in local extracellular potassium concentration, leading to enhanced drug-induced inhibition of IKr (rapidly activating delayed rectifier potassium channel). In none of the cases could it be established that pimavanserin alone contributed to QT prolongation, and in many

cases, it could not be confirmed that patients actually had QT prolongation compared to their pre-treatment state.

3.1.3.3. Representative Cases of Syncope or Loss of Consciousness

FAERS Case #12938564, Version 3, Expedited, Non-Solicited
PTs *Syncope, Pulmonary thrombosis, Vena cava thrombosis, Fall*
The patient was a 75-year-old female with PDP. Concomitant medications were citalopram and carbidopa/levodopa. Pimavanserin 34 mg daily was started on Day 1. The report was received on Day 42. On an unspecified date and duration of pimavanserin treatment, the patient was hospitalized secondary to "two fainting spells." These events are not described further. The patient was found to have pulmonary thrombosis and vena cava thrombosis. The patient was treated with tissue plasminogen activator. No other information was provided.

Reviewer's Comment: The case contained limited information. It is not possible to establish a diagnosis for the episode or a relationship between the AEs and treatment with pimavanserin. Pulmonary thrombosis and vena cava thrombosis possibly contributed to the events considered "fainting spells."

FAERS Case #13005355, Version 2, Expedited, Non-Solicited
PTs *Syncope, Narcolepsy*
This was submitted by a patient who was a 54-year-old female with psychotic disorder and hallucinations. Medications included ondansetron, tizanidine, tramadol, topiramate, hydrocodone, insulin, metoprolol, clonazepam, gabapentin, and donepezil. No other medical history was provided. The patient was treated with pimavanserin 34 mg for approximately one month. The patient stated that pimavanserin caused her to be "narcoleptic" and that she would frequently "fall asleep at the drop of a hat" and have numerous "fainting spells." The patient stated that she was not evaluated for the episodes. She decreased her dose to 17 mg, without resolution of sedation. After discontinuing pimavanserin, the sedation and fainting spells resolved.

Reviewer's Comment: It does not seem likely that these are actually syncopal episodes, rather than excessive sedation; however, the possibility that these are syncopal episodes cannot be ruled out. Several of the patient's medications can cause QT prolongation, including pimavanserin, ondansetron, and donepezil. The patient was treated with numerous drugs that can cause sedation and central nervous system (CNS) depression: tramadol, hydrocodone, topiramate, clonazepam, gabapentin. Pimavanserin can also cause sedation and CNS toxicity, including confusional state and probably encephalopathy and delirium. It is difficult to determine a diagnosis of her condition; the differential diagnosis includes at minimum: syncope, presyncope, sedation, general CNS depression, arrhythmia, and hypotension.

FAERS Case #12938025, Version 1, Non-Expedited, Non-Solicited
PTs Syncope, Heart rate decreased
This was a non-serious case submitted by the patient's nurse. The patient was an 81-year-old female with a diagnosis of PDP, hallucinations and delusions. She was treated with pimavanserin

34 mg for approximately three or four days. Other medical history and medication history were not provided. The nurse reported that the patient had experienced a syncopal episode and decreased heart rate while treated with pimavanserin. No other details were provided.

Reviewer's Comment: No other information was provided about the events or medical history. It is possible that this was a syncopal episode or another type of event related to LOC. There is a broad differential diagnosis for such events. It is possible that pimavanserin could have contributed through QT interval prolongation; however, there is no supportive information available. This is a representative case illustrating the limited information provided and resultant difficulty in assessing the potential role of pimavanserin.

FAERS Case #12703527, Version 2, Expedited, Non-Solicited

PTs *Loss of consciousness, Encephalopathy, Gait inability, Aphasia, Loss of personal independence in daily activities*

The patient was a 61-year-old male with PDP, dementia, hallucinations, and delusions, treated with pimavanserin 34 mg daily. On Day 1 of pimavanserin treatment, the patient was "knocked out cold, could not talk, couldn't feed himself or walk." Pimavanserin was discontinued because of these AEs. Concomitant medications included donepezil, carbidopa/levodopa, memantine, and rotigotine.

Reviewer's Comment: With the limited information, it is not possible to establish whether the event consisted of a LOC, or whether the events are more consistent with encephalopathy, delirium, profound CNS depression, or some other type of CNS event impacting cognitive and motor function. Pimavanserin can cause confusional states, sedation, and possibly encephalopathy and delirium. Given the apparent acuity and short time to onset relative to beginning treatment with pimavanserin, it is possible that pimavanserin caused or contributed to the CNS AEs.

Syncope is defined as a transient loss of consciousness (TLOC) caused by a period of inadequate cerebral nutrient flow, most often caused by an abrupt drop of systemic BP.[32] Syncope is only one of many potential causes of TLOC. True syncope itself has many possible causes, and there is a broad differential for diagnosing events consistent with TLOC, and distinguishing these conditions from true syncope may be challenging. The causes of TLOC resulting in syncope are grouped into 4 major categories: 1) neurally-mediated reflex syncope; 2) Orthostatic syncope; 3) Cardiac arrhythmias; and 4) Structural cardiopulmonary disease. The evaluation of suspected syncope relies heavily on obtaining a comprehensive history, performing a physical examination, and reviewing an ECG.[33]

In the FAERS cases coded with the PTs *Syncope* and *Loss of consciousness*, information was typically limited regarding the nature of the events, preceding events, medical history, additional potential risk factors, duration of the event, mental status examination, cardiac exam, or ECG. Thus, diagnosis and causality assessment were limited for most of the relevant FAERS cases. In addition, many patients experiencing TLOC or syncope have multiple co-morbidities that can contribute to TLOC; the PDP patient in these cases generally had numerous relevant medical conditions and medications. Thus, there may have been multiple plausible causes.

Most of these FAERS cases did not appear to include primary cardiac events; however, some appeared to be consistent with LOC. There were no reports of abrupt falls or injuries after fall or LOC. In numerous cases, it appeared that the patient had not fully lost consciousness; rather, it appeared that patients had experienced significant acute changes in mental status, which appeared more consistent with encephalopathy, confusional states, delirium, fluctuation in level of consciousness, or profound CNS depression or sedation, often accompanied by significant motor or speech impairment, and general incapacitation. Numerous (13) cases involving similar events were reported as "catatonia." In fact, pimavanserin was demonstrated in placebo-controlled trials to cause confusional states, hallucinations, and gait disturbance, at higher rates than in the placebo group. In addition, the following CNS postmarketing AEs have been reported very commonly during treatment with pimavanserin: *Fall, Confusional state, Gait inability, Asthenia, Somnolence, Abnormal behavior, Unresponsive to stimuli, Loss of consciousness, Immobile, Speech disorder, Delirium, Coma, Catatonia, Encephalopathy*. Because of the typical challenges with interpreting FAERS reports, it is not currently possible to conclude that all of these events were related to pimavanserin; however, it is possible that pimavanserin may increase the risks of these CNS events.

In most cases coded with the PTs Syncope or Loss of Consciousness, there was not a clear temporal relationship between the events and pimavanserin initiation to strongly suggest that pimavanserin was a causal factor. In addition, numerous patients had pre-existing major risk factors for syncope and pre-syncope, including orthostatic hypotension and treatment for orthostasis, autonomic instability, and diabetes mellitus. Similarly, patients with advanced PD and PDP are at high risk for falls, changes in mental status, sedation, and confusional states, secondary to their primary neurologic illness and medication treatments for PD and co-morbid conditions. Thus, many of these patients had numerous risk factors for events coded as syncope or LOC.

It is possible that some of the syncope or LOC AEs were related to treatment with pimavanserin, secondary to QT interval prolongation and arrhythmia; however, QT prolongation and arrhythmia were not reported in these cases. In addition, it is possible that some syncopal and pre-syncopal events could be related to pimavanserin through mechanisms causing autonomic instability (e.g., BP decreases and bradycardia). It appears that some events coded as syncope or LOC were not actually syncopal or LOC events, but were more consistent with encephalopathy or delirium, without full LOC. Some of these events appeared to be related to pimavanserin, based on temporal relationships, acute onset of events, and the premarketing findings of increased rates of confusional states with pimavanserin, compared to placebo.

3.1.4. Other Events of Interest

The FAERS search retrieved 112 reports for seizure, CVA, MI, or venous thromboembolism (VTE). See **Appendix B Table 8.2.3** for the FAERS search strategy for these cases. After accounting for duplicates (2) and excluding overlapping reports from **Sections 3.1.2** (38) and **3.3.2** (5), we included 67 cases in this section. **Table 3.1.4.1** summarizes 67 FAERS cases reporting non-fatal seizure, CVA, MI or VTE. See **Appendix E** for a line listing of these 67 cases.

Table 3.1.4.1. Descriptive Characteristics of Non-Fatal FAERS Cases reporting Seizure, CVA, MI or VTE for Pimavanserin, Received by FDA through March 4, 2018 (n=67)

	Seizure (n=27)	CVA (n=21)	MI (n=8)	VTE (n=11)
Sex				
Male	18	11	5	5
Female	8	10	2	6
Not reported	1	0	1	0
Age (years)	(n=25)			
Mean	76.9	79.9	74.2	72.5
Range	57-90	63-93	65-82	60-81
Duration of therapy	(n=10) 2 days- 2 months	(n=6) 3 days- 1.5 months	(n=3) 2 weeks – 6 months	(n=2) 11 days - ≤1 month
Time to onset from initiation	(n=19) Same day- 5 months	(n=18) 3 days- 6 months	(n=7) 7 days- 6 months	(n=9) 7 days – 14 months
Other risk factors				
Medical history of the event	2	0	1	1
Risk factors for the event	0	5†	0	4‡
Use of concomitant medication labeled for the event	16*	0	0	0

* Each case may report more than one: carbidopa/levodopa (9), quetiapine (6), donepezil (3), alprazolam (2), mirtazapine (2), sertraline (2), trazodone (2), aripiprazole (1), citalopram (1), fluoxetine (1), methylphenidate (1), paroxetine (1), perphenazine (1), rivastigmine (2), trihexyphenidyl (1)

† Include MI (1), atrial fibrillation/heart arrhythmias (2), aortic valve replacement (1), cancer (1)

‡ Include essential thrombocytosis (1), immobilization (3)

Definitions: CVA=Cerebrovascular Accident; MI=Myocardial infarction; VTE=Venous thromboembolism

For non-fatal cases reporting seizure, CVA, MI, or VTE [DVT (3), PE (6), both DVT and PE (2)], the majority of cases were solicited cases [solicited cases (44) and non-solicited cases (23)] and did not provide enough information to assess drug-event causality. Most patients were male with an age range of 57 to 93 years. Some cases reported past medical history, risk factors for the events of interest, or concomitant use of medications labeled for the event of interest. Duration of therapy and time–to-onset of event after beginning pimavanserin treatment ranged from days to months.

We summarized cases that provided the most information reporting seizure, CVA, MI or VTE from the case series.

FAERS Case #13025415, Version 1, Expedited, Non-Solicited

A 57-year-old female with an unknown medical history started pimavanserin for PDP. After two doses of pimavanserin, the patient experienced a seizure. Pimavanserin was discontinued, and quetiapine was weaned off at the same time. This case did not provide further information.

Reviewer's Comment:
This case reported seizure in a patient who received two doses of pimavanserin. Due to concomitant use of a medication labeled for seizure and lack of clinical details, including medical history, we were not able to determine the role of pimavanserin in the seizure.

FAERS Case #13867553, Version 3, Expedited, Solicited
A 77-year-old male with a history of aortic aneurysms and aortic valve replacement started pimavanserin for PDP. Two months later, the patient was admitted to a hospital due to a stroke. The patient was discharged on an unspecified date. This case did not provide further information.

Reviewer's Comment:
This case reported stroke in a patient who used pimavanserin for 2 months. The patient had a history of aortic valve replacement, which is a risk factor for developing stroke. Due to the underlying risk for stroke and a lack of clinical details, we were not able to determine the role of pimavanserin in the stroke.

FAERS Case #13743318, Version 1, Expedited, Solicited
A 73-year-old male with a history of nose bleed started pimavanserin for PDP. About three weeks later, the patient experienced chest pain and hypertension, and was admitted to the hospital overnight. The patient had "borderline first degree heart block on ECG" and received Nitropaste. Three days later, the patient experienced chest pain again with arm/shoulder pain. The patient had a "heart attack" and was admitted to hospital. The patient was discharged after five days. This case did not provide further information.

Reviewer's Comment:
This case reported a "heart attack" in a patient who received pimavanserin for about three weeks. This case did not provide information regarding past medical history other than nose bleed, or a list of concomitant medications. Due to lack of clinical details, we were not able to determine the role of pimavanserin in the event.

FAERS Case #13386105, Version 2, Expedited, Solicited
A 64-year-old male with a history of hypertension and hyperlipidemia started pimavanserin for PD. About a month later, the patient presented to the hospital with chest pain and shortness of breath, and was found to have bilateral popliteal DVT and bilateral PE with mild right-sided heart strain and demand ischemia. The patient was started on rivaroxaban and discharged to a nursing home seven days after hospital admission.

Reviewer's Comment:
This case reported DVT and PE in a patient who received pimavanserin for about one month. This case did not provide information regarding risk factors for DVT/PE such as family history, smoking status, prolonged bed rest or acute injury. Due to lack of clinical details, we were not able to determine the role of pimavanserin in the DVT/PE.

3.1.5. Off-Label Use

The FAERS search retrieved 93 reports coded with the PT *Off label use*. See **Appendix B Table 8.2.4** for the FAERS search strategy. After accounting for duplicates (1) and excluding cases reporting PDP as the reason for use (45), 47 cases were included in this section (categorized by PD, NOS and non-PD). Note: In an effort to provide the full description of cases with the PT *Off label use*, overlapping cases from other sections of this review were not excluded. See **Appendix F** for a line listing of these 47 cases.

Table 3.1.5.1. Descriptive Characteristics of FAERS Cases with PT *Off label use* for Pimavanserin, Received by FDA through March 4, 2018 (N=47)

	PD, NOS (n=12)	**Non-PD (n=35)**
Sex		
Male	10	19
Female	2	16
Age (years)	(n=11)	(n=34)
Mean	71	74
Range	49-85	47-95
Reasons for Use*	(n=12)	(n=35)
PD	12	0
Dementia	7	19
Alzheimer's	1	3
Generalized psychotic/Mental disorder	0	7
Hallucination, NOS	0	2
Others†	0	5
Serious Outcome*‡	(n=12)	(n=35)
Death§	4	19
Hospitalized	5	13
Other Serious	7	12
Causes of death§	(n=4)	(n=19)
Not reported	3	13
Underlying disease/Natural cause	0	3
COPD	1	0
Liver failure	0	1
MI/Heart attack	0	1
Pneumonia	0	1
Concomitant medications		
Reported	10	23
Not reported	2	12
Concomitant antipsychotic*	(n= 6)	(n=7)
Quetiapine	5	3
Risperidone	1	1
Ziprasidone	0	2
Aripiprazole	0	1
Haloperidol	0	1

* Each case may report more than one

Table 3.1.5.1. Descriptive Characteristics of FAERS Cases with PT *Off label use* for Pimavanserin, Received by FDA through March 4, 2018

(N=47)

	PD, NOS (n=12)	Non-PD (n=35)

† Include mania without psychotic symptoms (1), muscle weakness (1), torticollis (1), chronic myeloid leukemia (1), and disturbances of salivary secretion (1)

‡ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events.

§ Death cases overlap with cases from **Section 3.1.2**

Definitions: COPD=Chronic obstructive pulmonary disease; MI=Myocardial infarction; NOS=Not otherwise specified

The most common reported off-label reasons for use were dementia (with or without PD) and general psychotic/mental disorder. Most patients were male in the PD, NOS category, but similar between male and female in the non-PD category. The patients' age ranges were similar between non-PD use and PD, NOS use. Most of the cases reported use of concomitant medications including antipsychotics. Among 13 cases that reported concomitant antipsychotic use, eight cases reported use of quetiapine. Twenty-three cases [PD, NOS (4) and non-PD (19)] reported death; however, the majority of the cases did not provide causes of deaths or other clinical details to assess drug-event causality. See **Section 3.1.2** for more details on all death cases in this case series.

3.1.6. Patients < 65 Years of Age

The FAERS search retrieved 96 reports with a serious outcome for patients with <65 years of age. See **Appendix B Table 8.2.5** for the FAERS search strategy for these cases. After accounting for duplicates (3), 93 cases were included in this section. Note: In an effort to provide the full description of cases with a serious outcome for patients < 65 years of age, overlapping FAERS cases from other sections of this review were not excluded. See **Appendix G** for a line listing of these 93 cases.

Table 3.1.6.1. Descriptive Characteristics of FAERS Cases of Patients < 65 Years of Age for Pimavanserin, Received by FDA through March 4, 2018

(N=93)

Sex	
Male	60
Female	33
Age (years)	
17 - <30	1
30 - <40	2
40 - <50	3
50 - <60	29
60 - <65	58
Reasons for Use	
PDP	55
PD, NOS	26

Table 3.1.6.1. Descriptive Characteristics of FAERS Cases of Patients < 65 Years of Age for Pimavanserin, Received by FDA through March 4, 2018

(N=93)

PD with dementia	1
Dementia	2
Psychotic disorder, NOS	4
Others*	2
Not reported	3
Serious Outcomes[†‡]	(n=93)
Death[§]	27
Hospitalized	51
Disability	1
Other Serious	29
Causes of Death[§]	(n=27)
Not reported	18
PD	3
COPD	1
MI	1
NMS	1
Pneumonia	1
Postoperative complication	1
PE	1
Concomitant medications	
Reported	56
Not reported	37
Concomitant antipsychotics[†]	(n=22)
Quetiapine	18
Haloperidol	3
Clozapine	2
Olanzapine	1
Risperidone	1

*Include drug-drug interaction study (1), and torticollis (1)

[†] Each case may report more than one

[‡] For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events.

[§] Death cases overlap with cases from **Sections 3.1.2 and 3.1.3.**

Definitions: COPD=Chronic obstructive pulmonary disease; MI=Myocardial infarction; NMS=Neuroleptic Malignant Syndrome; NOS=Not otherwise specified; PD=Parkinson's disease; PDP=Parkinson's disease psychosis; PE=Pulmonary embolism

The majority of patients were male, with an age range from 50 to <65 years. Most cases reported the reason for use as PDP, and reported concomitant medication use. Among 22 cases that reported concomitant antipsychotics use, 18 cases reported use of quetiapine. Of 27 cases that reported death, 26 cases reported patients age ranged between 50 and <65 years. The remaining one fatal case reported a 46-year-old patient with PD developed fever and "shakes,"

then died from "complication of illness." The majority of fatal cases did not provide the cause of death or other clinical details to assess drug-event causality. See **Sections 3.1.2** and 3.1.3 for more details on all death cases in this case series.

For five non-fatal cases reporting patients <50 years of age, four cases reported the reason for use including PD, NOS (2), PDP (1), and psychotic disorder, NOS (1). These cases reported involuntary movements of face and jaw, paranoia and hallucination, peripheral swelling and bloating, and aggression. The time-to-onset of AEs ranged from the same day to two months after starting pimavanserin. Pimavanserin was discontinued in these cases, and one case reported resolution of peripheral swelling and bloating. The other cases did not report whether the AEs resolved after pimavanserin discontinuation. The remaining one non-fatal case of a patient <50 years of age reported receiving pimavanserin during a drug-drug interaction study with rifampin. Eighteen days after the second dose of pimavanserin (four days after the last dose of rifampin), the patient developed confusional state and was hospitalized for evaluation of new onset psychosis.

3.2. DRUG UTILIZATION

To provide context for the AE reports submitted to the FAERS database, U.S. drug utilization patterns for pimavanserin were assessed using the Sponsor-provided data from June 2016 through March 2018.

3.2.1 Number of Tablets[34]

Table 3.2.1.1 below displays the total number of tablets distributed for Nuplazid in the U.S., stratified by channel, from June 2016 through March 2018. During this time, approximately (b) (4) tablets were distributed with nearly (b) (4)% ((b) (4) tablets) going to specialty pharmacies, followed by (b) (4)% (b) (4) tablets) to specialty distributors.

Table 3.2.1.1 Total Number of Tablets Distributed for Nuplazid, Stratified by Channel in the U.S., from June 2016 Through March 2018, Cumulative

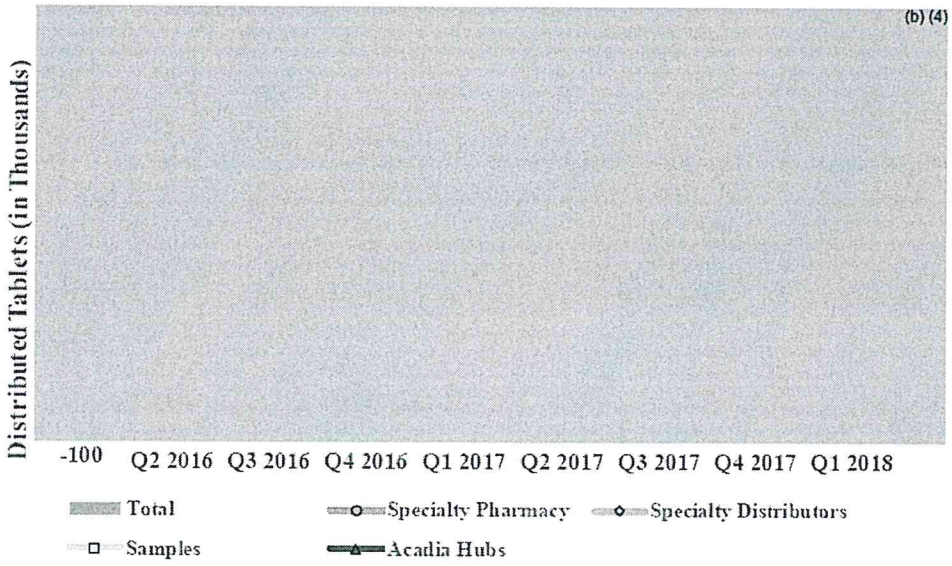
NUPLAZID Tablet Volume by Channel	Tablets	% of Total Volume
Total	(b) (4)	100%
Specialty Pharmacy (SP)[1]		(b) (4)%
Specialty Distributors (SD)[2]		%
Samples[3]		%
ACADIA HUB[4]		%

[1] Specialty Pharmacy (SP) is all mail-order. Four SPs are currently used: CVS, ACS, Walgreens, Accredo.
[2] Specialty Distributor (SD) volume includes tablets shipped from SDs to Group Purchasing Organization (GPO) member pharmacies that service Long Term Care (LTC) and non-GPO member pharmacies that service LTC, Tricare, Veteran Affairs (VA) Hospital, and Kaiser. Four SDs are currently used: McKesson, AmerisourceBergen, Cardinal, HD Smith.
[3] Sample volume represents volume of samples provided to physician's offices, not volume dispensed to patients.
[4] ACADIA HUB volume includes tablets shipped to patients through Free Trial or Patient Assistance Programs (PAPs).

Figure 3.2.1.1 shows the number of tablets distributed for Nuplazid in the U.S., stratified by channel, from Q2 2016 through Q1 2018. Specialty pharmacies accounted for approximatel (b) (4)% ((b) (4) tablets) of total tablets in the second quarter of 2016, increasing to (b) (4)% (b) (4) ablets)

in the first quarter of 2018. Tablets distributed by specialty distributors accounted fo (b) (4) ((b) (4) tablets) of total tablets in the second quarter of 2016, increasing to (b) (4) % (b) (4) tablets) in the first quarter of 2018.

Figure 3.2.1.1 Total Number of Tablets Distributed for Nuplazid in the U.S., Stratified by Channel, from Q2 2016 Through Q1 2018



3.2.2 Number of Patients[34]

Table 3.2.2.1 and **Table 8.8.1** in **Appendix H** displays the total number of unique patients in the U.S. who received a prescription for Nuplazid, from June 2016 through March 2018, cumulative and quarterly, respectively. For the cumulative time, approximately (b) (4) patients received a prescription for Nuplazid. Of the total (b) (4) patients, patients aged 70-79 years accounted for nearly (b) (4) % of total patients (b) (4) patients), followed by patients aged 80 years and older who accounted for (b) (4) % of total patients (b) (4) patients). Similar proportions of use were observed in the quarterly patient data shown in **Appendix H**.

Table 3.2.2.1 Total Number of Unique Patients Who Received a Prescription for Nuplazid, Stratified by Age Groups and Pharmacy Setting of Care in the U.S., from June 2016 Through March 2018, Cumulative

	June 2016 Through March 2018	
	Patient (N)	Share (%)
Total NUPLAZID[1]	(b) (4)	100%
0-9 years		(b) (4)
10-19 years		
20-39 years		
40-59 years		
60-69 years		
70-79 years		
80+ years		
18-45 years*		
46-65 years*		
66-88 years*		
89+ years*		
Unknown Age[2]		
Total NUPLAZID[1]		100%
Mail-order/Specialty		(b) (4)
ACADIA HUB[3]		
Long-term care[4]	Patient Count Not Available	
Outpatient-retail	Not Applicable	

[1] Includes all unique patients who received Nuplazid from specialty pharmacy (SP) or through free trial or patient assistance programs (PAP)
[2] Unknown age represents known unique patients who were shipped Nuplazid through free trial or PAPs but were not serviced by a SP.
[3] Acadia Hub includes unique patients who received Nuplazid through free trial or PAPs but never received Nuplazid from SP, to avoid double counting.
[4] Long-term care (LTC) patients obtain Nuplazid from LTC pharmacies.
* Patient year of birth were not available for the unique patients listed under these age groupings.

3.3. Other Data Sources

3.3.1. PADER

During the reporting period October 29, 2017 to January 28, 2018, the Sponsor received 1,509 reports including 206 fatal reports. Forty-two reports provided the causes of death and the most common causes reported were PD/dementia followed by pneumonia, cardiac related/sudden death, CVA, respiratory failure/COPD, and MI. The Sponsor concluded that the review of fatal reports reflected common morbidities and end of life events in this population, and there was no consistent pattern.

The Sponsor stated that because of their distribution model, there is frequent contact with outpatients by the Sponsor's reimbursement hub and specialty pharmacies, and these frequent

contacts account for the main source of reported AEs. They also calculated a "mortality rate" for the reporting period based on shipments supplied by specialty pharmacies to unique patients.

Reviewer's Comment:
As the Sponsor described, frequent contact with consumers will likely stimulate postmarketing AE reports. Due to lack of clinical details provided in these reports and several underlying risk factors for death in this patient population with PDP, we are not able to determine drug-event causality. See ***Sections 2.3.3*** *and* ***3.3.3*** *for further details on the Sponsor's "mortality rate."*

3.3.2. Thorough QT Study

Design: This was a double-blind, placebo-controlled and positive-controlled (moxifloxacin), 4-arm, multiple-dose parallel design evaluation of QT/QTc interval effects of pimavanserin 20 mg and 80 mg doses once daily in 252 healthy adult subjects after 20 consecutive days of dosing. Study drug was administered for up to 20 days. The four treatment groups included pimavanserin 20 mg (clinical dose), pimavanserin 80 mg (supratherapeutic dose), placebo plus moxifloxacin 400 mg (moxifloxacin on Day 20 only), and placebo. The study included a screening period of up to 30 days that included two days of baseline assessments (Days -2 and -1), a 20-day double-blind treatment period, a final study visit (Day 21) or early termination, pharmacokinetic (PK) sample visits on Days 21 through 24, and a follow-up telephone visit on Day 35 (±2 days). On Day 1, subjects were randomized to receive pimavanserin 20 mg, pimavanserin 80 mg, placebo/moxifloxacin 400 mg, or placebo daily for 20 days. Subjects randomized to the placebo/moxifloxacin group received placebo for Days 1 through 20 plus moxifloxacin 400 mg on Day 20 only.

The Sponsor provided an acceptable justification for the doses selected. The worst-case scenario is illustrated by cytochrome P450 enzyme (CYP) 3A4/5 inhibition with ketoconazole where exposure to pimavanserin increased 1.5-fold for the peak serum concentration (Cmax) from 17.1 to 25.1 ng/mL, and 3-fold for the area under the concentration curve (AUC_{0-24}) from 1224 to 3415 ng·h/mL in Study ACP-103-023. These increases are well-covered by available safety and associated exposure data in humans where single doses of up to 300 mg and multiple doses of up to 150 mg for 14 days have resulted in Cmax values of up to 152 ng/mL (300 mg single dose) and 248 ng/mL (150 mg for 14 days) and corresponding AUCs of up to 10,798 and 4,680 ng·h/mL. At doses ≥100 mg, AEs of dizziness, somnolence, lethargy, nausea, vomiting, dyspepsia, epistaxis, back pain and fatigue have been reported with pimavanserin at rates at least twice those for placebo.

The supratherapeutic dose of 80 mg pimavanserin tested in the TQT study also encompasses the exposures seen when pimavanserin 40 mg was coadministered with ketoconazole. The 80-mg dose was associated with Cmax values of 49.43 and 205.92 ng/mL and AUC values of 860.3 and 3817.1 ng·h/mL at Day 1 and Day 20, respectively. The TQT study also tested pimavanserin 20 mg, moxifloxacin, and placebo and across the four dose groups, the most common treatment-emergent adverse event (TEAE) across treatment groups was headache (13.3%, pimavanserin 20 mg; 22.2%, pimavanserin 80 mg; 22.0%, placebo/moxifloxacin; 19.7%, placebo). Events that occurred in >5% of subjects included headache in the pimavanserin 20 mg, headache, dizziness (15.3%), nausea (12.5%), and rash (5.6%) in the pimavanserin 80 mg group, headache,

pharyngolaryngeal pain and diarrhea (5.1%) in the placebo/moxifloxacin group, and nausea (6.6%) in the placebo group. Events that occurred in ≥10.0% of pimavanserin 80 mg-treated subjects and twice the incidence of pimavanserin 20 mg-treated subjects included nausea (12.5% vs. 1.7%) and dizziness (15.3% vs. 3.3%).

Reviewer's Comment: The studied doses are acceptable. The study result is positive. Although the therapeutic dose (40 mg daily) was not directly studied in this TQT study, the studied exposure range covered the clinically relevant exposure.

Overall summary of findings: **Table 3.3.2.1** summarizes the findings below. Using QTcI correction, a marginal QTc prolongation effect of pimavanserin at the 80-mg dose once daily after 20 consecutive days of dosing was detected in this TQT study. The largest upper bound of the two-sided 90% CI for the mean difference between pimavanserin 80 mg and placebo is 16.6 ms at 6 hours postdose on Day 20. The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in **Table 3.3.2.1.**, indicating that assay sensitivity was established. The therapeutic dose of 40 mg once daily for pimavanserin is not directly studied in this TQT trial. Based on the linear PK of pimavanserin, the 80-mg dose studied in this study is expected to provide a 2-fold margin over the therapeutic exposure. CYP3A4/5 inhibitor ketoconazole increases pimavanserin Cmax 50% and triples AUC in the single-dose study. The effect of hepatic impairment and renal impairment on pimavanserin PK are unknown. Based on the concentration-QTc relationship, a marginal QTc prolongation is expected at the therapeutic concentration.

Table 3.3.2.1. The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Pimavanserin (20 mg and 80 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
Pimavanserin 20 mg	1	4.4	(1.6, 7.2)
Pimavanserin 80 mg	6	13.5	(10.3, 16.6)
Moxifloxacin 400 mg*	4	11.2	(8.2, 14.2)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 7.1 ms.

The results of the TQT study informed decisions about labeling for the following sections: Warnings and Precautions, Drug Interactions, and Pharmacodynamics. The QT-IRT provided recommendations for labeling language.

3.3.3. Sponsor's IR Response[23-25]

The Sponsor's response included an analysis of all fatal pimavanserin AE reports received by the Sponsor from April 29, 2016 (FDA approval date) through February 28, 2018. During this period, 885 fatal AE reports were received by the Sponsor, and were included in their analysis.

An estimated (b) (4) patients were exposed to pimavanserin since the commercial launch of the drug (May 31, 2016) through February 28, 2018, with an estimated (b) (4) patient-years of exposure.

Overall, the Sponsor was unable to identify a causal relationship between pimavanserin and any specific AE that resulted in death. Following are highlights of the Sponsor's analysis and conclusions:

- The majority of the distribution of pimavanserin to patients is through specialty pharmacies (b) (4)%). Approximately (b) (4)% of AE reports received by the Sponsor are considered solicited reports from frequent contacts with consumers by the Sponsor's reimbursement hub and specialty pharmacy network. The Sponsor claims that this distribution mechanism for pimavanserin results in a larger number of AE reports to the Sponsor "than would be expected via routine voluntary spontaneous [non-solicited] reporting."

DPV-I Reviewer's comment:
A sponsor that has more frequent contact with consumers via reimbursement hubs, patient assistance programs, specialty pharmacies, or any other patient support programs is likely to stimulate more AE reports than a sponsor that does not have frequent contact with consumers via these mechanisms. The seemingly large number of death reports observed with pimavanserin may reflect solicited reporting and prescribing to elderly patients with advanced PD who may have multiple risk factors for death.

- The Sponsor used the total of spontaneous and solicited reports of death (n=885) as the numerator, and patient-years of exposure in the U.S. population estimated from distribution data as the denominator (n=6,205 patient-years), to calculate a "mortality rate" of 14.26 deaths per 100 person-years (95% CI: 13.34, 15.23). The Sponsor compared this "mortality rate" with other mortality rates per 100 patient-years derived from different sources:
    - The Sponsor's clinical trials (Phase 2 and 3 double-blind, placebo-controlled studies in PD and Alzheimer's disease; placebo: n=357; pimavanserin: n=510): The Sponsor's table below is reproduced from their response to our IR, received by FDA April 19, 2018. Deaths occurring within 30 days of the last dose of study treatment were included. (The Sponsor also notes that there were no deaths in Phase 1-type studies.)

Table 1 Summary of Deaths: Phase 2/3 PD/PDP/ADP Clinical Studies[1] Completed by End of 2016 (Safety Analysis Set)

Statistics	Placebo	PIM[2]
Total Number of Subjects	357	510
Number of Deaths[3]	5	6
Person-Years (PY) of Exposure[4]	45.8	60.0
Mortality Rate per 100 PY	10.9	10.0
95% CI of Mortality Rate per 100 PY	(3.5, 25.5)	(3.7, 21.8)

Abbreviations: ADP=Alzheimer's disease psychosis; CI=confidence interval; PD=Parkinson's disease; PDP=Parkinson's disease psychosis; PIM=pimavanserin; PY=person-years

1 Study treatment period ≤12 weeks.

2 ACP-103-005, -006, -012, -014, -020, (b) (4) including fixed doses of PIM 8.5 mg (-012, -014), 17 mg (-014), 21 mg (-005), 34 mg (-012, -020, (b) (4)), 85 mg (-005) and flexible-doses of 17-51 mg (-006).

3 Deaths that occurred within 30 days after last study dose date.

4 Total cumulative person-years on study medication.

- Mortality rates for patients with PD taking antipsychotics published in the medical literature: Weintraub et al. studied patients with PD on antipsychotic medications. Their retrospective cohort study in the Veterans Health Administration[19] examined mortality in a cohort of 7,877 medically stable patients with PD with a mean age of 76 years who began antipsychotics, compared to a matched sample of patients with PD not using antipsychotics. Antipsychotics were associated with higher mortality (hazard ratio 2.4, 95% confidence interval 2.1-2.7 compared to non-use). In absolute terms, the mortality with antipsychotic use ranged from 51 per 100 patient years with haloperidol to 12 per 100 patient years with "other" atypical antipsychotics.

The Sponsor also included an abstract from a recently completed observational study utilizing U.S. Medicare data from January 1, 2012 to December 31, 2015. The purpose of the study was to determine the background mortality rates and comorbidities in patients with PD with and without psychosis. The results are provided in **Table 3.3.3.1** below.

Table 3.3.3.1. Mortality Rates in Patients with Parkinson's Disease with and Without Psychosis	
U.S. Medicare Data (January 1, 2012 – December 31, 2015)	Age Standardized Mortality Rates per 100 Person-Year of Follow Up per U.S. Census 2010 (95% CI)
Parkinson's disease	7.31 (7.15-7.47)
Parkinson's disease psychosis	28.18 (27.53-28.8)

Taking all of these data sources together, the Sponsor concludes that patients with PDP "are at higher risk of death, and that postmarketing mortality rates for [pimavanserin] are consistent with what is seen in the general PDP population."

DPV-I Reviewer's Comment:

The "mortality rate" the Sponsor calculated from the postmarketing reporting rate is not useful. We cannot estimate underreporting and control for the number of unreported deaths in patients exposed to pimavanserin, and therefore cannot estimate the accuracy of this "mortality rate." There is insufficient evidence to conclude that postmarketing mortality rates for pimavanserin are consistent with mortality rates in the general PDP population. The Sponsor does provide an abstract describing observational data showing patients with PDP are at higher risk of death compared to PD patients without psychosis. See DEPI-1 Reviewer's Comment below for additional details.

DEPI-I Reviewer's Comment:
The principle question is how closely the Sponsor's reporting rate for fatal AEs (which the Sponsor labels a "mortality rate") approximates the true mortality rate among pimavanserin users. The Sponsor estimated (b) (4) *patient-years of exposure through February 28, 2018 from the total days supply distributed to individual patients by specialty pharmacies (representing* (b) (4) *patient-years) and the total days supply distributed directly to patients as free product (representing* (b) (4) *patient-years). The Sponsor did not include product shipped to an institution or healthcare system that was not designated for specific patients. To the extent that the Sponsor's method of estimating exposed patient-years omits some pimavanserin use, that would reduce the numerator and thus bias the rate upwards. A far more salient concern, however, is under-reporting of deaths; the number of fatal AE reports represents some unknown fraction of the true number of deaths, and the smaller that fraction, the more the rate estimate is biased downward. The Sponsor argues that under-reporting of deaths is apt to be minimal because of the way pimavanserin is distributed, but the actual degree of under-reporting remains unknown.*

The Sponsor classifies reports of death through specialty pharmacies as "solicited" and other reports as "spontaneous." They state in their response to the April 13, 2018 IR that approximately 85% of all pimavanserin AE reports are "solicited." If we apply that percentage to the 885 fatal AE reports, it would suggest that 752 of the fatal reports were solicited and 133 were spontaneous. If one takes 752 solicited reports for the numerator and (b) (4) *patient-years of specialty pharmacy exposure as the denominator, the reporting rate for solicited reports of death is* (b) (4) *per 100 patient-years. This is indeed somewhat higher than the corresponding reporting rate for non-solicited reports (i.e., 133 spontaneous death reports with* (b) (4) *patient-years of non-specialty pharmacy exposure gives a reporting rate of* (b) (4) *per 100 patient-years). However, the difference between the two is likely to be even greater, as the Sponsor states that they did not start classifying solicited reports as such until January 29, 2017; i.e., some portion of the 133 "spontaneous" reports of death were actually from specialty pharmacy use prior to January 29, 2017. Accordingly, there is some support for the Sponsor's assertion that the specialty pharmacy distribution practices generate more reports of deaths, but it is still not possible to make reliable comparisons of those numbers to other data.*

The Sponsor's updated controlled clinical trial mortality data indicate that adding the Alzheimer's disease trial data to the Parkinson's trial data diminishes the numeric imbalance of deaths present in the original NDA submission [4 on pimavanserin (1%) and 1 (0.4%) on placebo in controlled trials][35]. However, from a quantitative standpoint the reassurance provided is limited; while the incidence rate ratio (pimavanserin:placebo) is 0.92, the 95% CI is wide (0.27-3.26)[36]. Additionally, patients with PD may have different tolerance for pimavanserin

from patients with Alzheimer's disease. The Sponsor's May 11, 2018 Sequence 0071 response to an April 13, 2018 IR provided an updated analysis of deaths in placebo-controlled trials, adding in two deaths on pimavanserin that occurred more than 30 days after the last dose, and data from recently completed trial (b) (4) *in Alzheimer's disease. The updated mortality rates per 100 person-years, with 5 deaths on placebo and 8 on pimavanserin, are 9.3 for placebo and 10.8 for pimavanserin (rate ratio 1.2, 95% CI: 0.38-3.9).*

- The most common cause of death reported among the fatal AE reports was death, NOS or unreported cause (n=590; 67%). The top five specified causes of death were advanced or end-stage PD/progression dementia (n=123; 14%), pneumonia/aspiration pneumonia (n=38; 4%), MI (n=19; 2%), cardio-pulmonary/respiratory failure (n=19; 2%), and sepsis (n=15; 2%). Mean age was 78 years (range 46-96). No consistent pattern or trend was identified among the causes of death, except that they were "reflective of the common comorbidities and end of life events common in this population."

DPV-I Reviewer's Comment:
It is typical for postmarketing reports to include limited clinical information on the cause of death. An evaluation of the case report involving the youngest patient in the analysis, a 46-year-old male (FAERS Case# 13880412), did not reveal a causal relationship between pimavanserin and the AE (i.e., causality was unassessable due to lack of information). Of note, the Sponsor reportedly documents follow-up attempts on fatal AE reports. See ***Section 3.1.2*** *for FAERS case summary.*

- The Sponsor conducted an analysis of individual case reports in which the cause of death was reported as one of the following: advanced or end-stage PD/progression of dementia-related (n=82), cardiac-related (n=54), CVA (n=10), pneumonia-related (n=36), cardio-respiratory/respiratory failure-related (n=19), and sepsis-related (n=15) (number of cases per cause of death is different from what is listed in the preceding bullet point because the Sponsor used different definitions for cause of death in their individual case analyses). Case reports across all the above listed causes of death had several limitations. The cases either lacked pertinent information to assess causality, or reported several confounders. Cases often did not include information on concomitant medications or medical history. Cases that did report such information revealed several confounders, such as multiple comorbidities (e.g., cardiovascular disease, diabetes, dementia), as well as concomitant medications (e.g., antipsychotics, antidepressants, donepezil, memantine, antihypertensives, antihyperglycemic drugs). The analysis also examined duration of therapy prior to the event, and did not identify any specific trends. The Sponsor concluded "there is no evidence of a causal relationship with [pimavanserin] and the overall risk/benefit profile for [pimavanserin] remains positive."

DPV-I Reviewer's Comment:
Incomplete reports and lack of a comparison group provide several limitations for assessing causality. After reviewing the postmarketing data included in the Sponsor's IR response, we

were unable to identify evidence of a causal relationship between pimavanserin and a specific pathophysiological process that hastens death.

4. DISCUSSION

Our review did not identify any new or unexpected safety findings with pimavanserin in the postmarketing safety analysis, compared to the safety profile established in the premarketing trials. DPV, DEPI-I and DEPI-II utilized the pimavanserin product labeling, top PTs reported for pimavanserin in FAERS, analysis of select FAERS cases, the Sponsor's PADER, the Sponsor's IR responses, the TQT study results, and relevant published medical literature on PD, PDP, and the use of antipsychotics in PD and dementia to provide information about potential safety risks reported with the use of pimavanserin.

To provide context for the FAERS reports, U.S. drug utilization patterns for pimavanserin were assessed using the Sponsor-provided data from June 2016 through March 2018. The majority of use was in elderly patients with approximately 35-39% of total patients who received Nuplazid prescriptions aged 70-79 years, followed by patients aged 80+ years accounting for approximately 27-30% of patients. In the second quarter of 2016, approximately (b) (4) total tablets were distributed to all settings of care, increasing to (b) (4) tablets in the first quarter of 2018. The number of tablets distributed to specialty pharmacies accounted for approximately (b) (4)% ((b) (4) tablets) of total tablets in the second quarter of 2016, increasing t (b) (4)% ((b) (4) ablets) in the first quarter of 2018.

Pimavanserin is almost exclusively distributed by specialty pharmacies and specialty distributors. Frequent contact with consumers via reimbursement hubs, patient assistance programs, or specialty pharmacies can explain the high number of postmarketing AE reports for pimavanserin. Drug utilization data and FAERS data showed patients aged 70 years or older accounted for the highest proportion of pimavanserin use.

The majority of FAERS cases were solicited by Nuplazid Connect or specialty pharmacies, and these cases often provided insufficient information to assess drug-event causality. Because of limited clinical details and the presence of several underlying patient risk factors, these postmarketing AE reports are challenging to interpret. In addition, FAERS data analysis generally cannot detect a drug-related increase or difference in events with high background rates or known drug-related events (e.g., death, other SAE, and QT effects). Our FAERS cases reported a wide range of time-to-onset of AEs in relation to pimavanserin treatment, and included patients having advanced PD with several underlying risk factors for death such as advanced age, multiple cardiovascular and other comorbidities, and multiple concomitant medications posing serious risks in PD patients, including antipsychotics. Antipsychotic use in elderly patients with dementia or PD increases the risk of all-cause mortality. Furthermore, numerous cases reported concomitant use of pimavanserin and other drugs that can prolong the QT interval, particularly antipsychotics and antidepressants.

Pimavanserin can also cause QT prolongation, and it may increase the risk of life-threatening arrhythmia; thus, it could have contributed to some of the reported cardiovascular SAEs. However, our review of FAERS cases did not capture any cases of TdP, other ventricular

arrhythmias, or any fatalities in the cases of reported QT prolongation. Most cases reporting QT prolongation had limited information, lacked baseline ECGs for comparison, and did not have confirmation of actual QT prolongation. In addition, many cases involved additional risk factors for QT prolongation, including MI, acute ischemia, or use of other QT-prolonging drugs (e.g. quetiapine, olanzapine, clozapine, paliperidone, citalopram, escitalopram, fluoxetine, and antiarrhythmics) or diuretics. It is possible that some of the cases reported as sudden death, cardiac arrest, syncope, and LOC were related to pimavanserin, secondary to QT prolongation; however, we do not have sufficient evidence (i.e., report of QT prolongation associated with these events) at this time to determine a causal relationship.

The DARS review team made several predictions about AEs that might be reported with postmarketing pimavanserin use, based on safety considerations with cyproheptadine, a serotonergic drug with some receptor pharmacology similarities with pimavanserin; however, the drugs do not have fully overlapping pharmacology. The DARS team concluded that pimavanserin could aggravate autonomic dysfunction (primarily BP lability), falls, and insomnia in some patients with PDP. They also noted that patients with PD are known to have these comorbidities secondary to their underlying disease process. For example, patients with PD commonly suffer from autonomic instability, including orthostatic hypotension, and they have multiple risk factors for falls. The pimavanserin controlled trials did not demonstrate increased rates of BP changes or abnormalities, falls, or insomnia. Postmarketing cases included reports for all of these AEs. However, we could not establish a causal role for pimavanserin in these cases, because all of these AEs occur commonly in patients with PDP as comorbid conditions secondary to PD pathophysiology or treatments for PD. In addition, the cases pertaining to BP abnormalities did not include clinically confirmed, objective vital sign data (pretreatment or on-treatment), there were multiple risk factors for BP changes, and there were few clear temporal relationships between AEs and pimavanserin. Only one case of syncope also reported low BP. Some of the most commonly reported postmarketing SAEs with pimavanserin included falls, confusional state, and gait abnormalities. Furthermore, the pimavanserin controlled trials demonstrated increased rates of gait disturbance and confusional states (compared to placebo), both of which can increase the risk of falls. Gait disturbance and confusional state are labeled in the Adverse Reactions section. However, given the limitations of the FAERS data described above, it was not possible to reach conclusions about a causal role for pimavanserin in these SAEs. There were postmarketing reports of insomnia, but we could not reach conclusions about causality for similar reasons. PDP patients commonly have sleep disturbances, and the cases were not conclusive.

In the controlled trials, pimavanserin was associated with an increase in all-cause mortality and all-cause SAEs, compared to placebo. However, there was no identified unifying mechanisms to explain the findings. Thus, in addition to its QT prolongation effects, it is possible that pimavanserin had a causal role in some of the fatalities and other SAEs during postmarketing use. However, there were no unexpected causes of deaths or other SAEs in the postmarketing cases, and there was no unifying biologic mechanism to explain the fatal or SAEs, consistent with the findings in the premarketing program.

The Sponsor's updated analysis of deaths in placebo-controlled trials (5 deaths with placebo and 8 with pimavanserin) found mortality rates per 100 person-years of 9.3 for placebo and 10.8 for

pimavanserin (rate ratio 1.2, 95% confidence limit 0.38-3.9), which is difficult to interpret because the estimate is imprecise. The Sponsor's "mortality rate" calculated from the postmarketing fatal event reporting rate must also be interpreted cautiously because the degree of underreporting of deaths is unknown, even if one allows that the distribution system for pimavanserin encourages reporting. Accordingly, this postmarketing "mortality rate" cannot be reliably compared to other sources of data, given the unknown amount of underreporting.

Although there were no new or unexpected safety findings, many patients with PDP in the FAERS cases were being treated concomitantly with pimavanserin and other QT interval-prolonging drugs, further increasing the risk of QT prolongation and life-threatening arrhythmias. Numerous patients were treated concomitantly with antipsychotics that can prolong the QT interval and have QT warnings, including: quetiapine, clozapine, asenapine, paliperidone, and iloperidone. Several patients were treated with the antidepressant, citalopram, which can cause QT prolongation. These QT-prolonging drugs are currently not discussed in pimavanserin labeling. It may be worthwhile to further emphasize these risks in the labeling along with a Drug Safety Communication.

5. CONCLUSIONS

Although we did not identify any new or unexpected safety findings with pimavanserin in the postmarketing analysis at this time, it may be worthwhile to further emphasize in labeling the risks of concomitantly administering pimavanserin with other QT interval-prolonging drugs. It may also be useful to consider a Drug Safety Communication discussing these risks.

6. RECOMMENDATIONS

Based on this review, OPE recommends the following:

- Revise the Warnings and Precautions (QT Interval Prolongation), and Drug Interactions sections to emphasize the increased risk of QT prolongation and life-threatening cardiovascular events when treating patients concomitantly with pimavanserin and other drugs that can prolong the QT interval. We recommend listing specific antipsychotics which are known to cause QT prolongation and have QT warnings (quetiapine, clozapine, asenapine, paliperidone, and iloperidone), as well as the antidepressant, citalopram, known to cause QT prolongation. All of these drugs were used concomitantly in the pimavanserin FAERS cases.
- Consider issuing a Drug Safety Communication to discuss these serious risks.
- Consider developing a Medication Guide to educate patients and caregivers about these risks.

DPV will continue to monitor all AEs for pimavanserin, with focus on trends in the death reports, AEs related to autonomic instability or CNS toxicity, and serious cardiovascular AEs.

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